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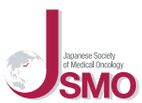
Abstract Book of the
42nd ESMO Congress (ESMO 2017)



Madrid, Spain
8–12 September 2017

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Late-breaking abstracts and abstracts selected for the **Press Programme** will be made public at 00:05 CEST (Central European Summer Time) on the day of the official Congress session during which they are presented.

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The European Society for Medical Oncology (ESMO)

ESMO is the leading professional organisation for medical oncology, with the overarching goal of improving outcomes for cancer patients everywhere. We are the society of reference for oncology education and information, and are committed to supporting our members to develop and advance in a fast-evolving professional environment.

Founded in 1975, ESMO has European roots with a global reach: we welcome oncology professionals from around the world. We are a home for all oncology stakeholders, connecting professionals with diverse expertise and experience, and speaking with one voice for our discipline. Our education and information resources support an integrated multi-professional approach to cancer care, from a medical oncology perspective. We seek to erase boundaries in cancer care, whether between countries or specialities, and pursue our mission across oncology, worldwide.

The ESMO community brings together more than 16,000 oncology professionals from over 130 countries. 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.

Please visit **esmo.org** to learn more. **Across Oncology. Worldwide.**

The European Association for Cancer Research (EACR)

The European Association for Cancer Research is a professional membership society for cancer researchers with more than 10,000 members worldwide. The EACR was founded in 1968 and has one guiding aim: 'The advancement of cancer research for the public benefit'. Membership is open to anyone actively working or studying in cancer research. Our members work across the full spectrum of the field, from basic through to translational and clinical research, and range from postgraduate students to winners of the Nobel Prize. Researchers who are members of one of the 14 EACR affiliated 'National Societies' automatically become members of the EACR as part of the wider benefits of belonging to their national society. The membership fee for active members is just 40 Euros per annum or 120 Euros for 4 years, and special reduced membership fees are available to postgraduate students and those with less than 4 years' post-doctoral experience.

We facilitate communication and collaboration within the cancer research community. We also set out to raise the profile of cancer research in Europe and to make the case for sustained political and economic support. We organise scientific conferences of the highest quality, open to members and non-members. Our Conference Series of small, focused meetings is highly regarded for its focus on the latest research topics and for the provision of opportunities for interaction between speakers and participants. In 2018 we will celebrate our 50th anniversary and invite you to join us at EACR25, our biennial Congress to be held in Amsterdam, Netherlands, 30 June - 03 July 2018.

Find out more about the EACR at **www.eacr.org**

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BASIC SCIENCE

1O Wild-type KRAS mediates growth inhibition and resistance to MEK inhibitors through dimerization with mutant KRAS in lung adenocarcinoma

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Background: Mutations in *KRAS* are the most frequent *RAS* alterations in human cancers and the prevalent driver event in lung adenocarcinoma (LUAD). There are no effective targeted therapies for KRAS-driven LUAD and chemotherapy remains the standard of care. Small-molecule inhibitors of the MAPK pathway, one of the prominent downstream KRAS mediators, show minimal clinical activity either as single agents or in combination with chemotherapy. Recently, wild-type KRAS ($KRAS^{WT}$) was shown to enhance tumor fitness in *KRAS* mutant AML and CRC cell lines while concomitantly increasing sensitivity to MEK inhibition. We hypothesized that dimerization between KRAS proteins could be a key regulator for lung adenocarcinoma biology and determinant of treatment response.

Methods: To study the role of wild-type *KRAS* in the context of KRAS-driven cancer cells, we used genetically inducible models of *KRAS* loss of heterozigosity (LOH). We developed an isogenic $KRAS^{MUT}$ inducible system that lacks endogenous *HRas/NRas* but harbors conditional CRE^{ERT2}-controlled $KRas^{lox}$ alleles. Furthermore, we reconstituted $KRAS^{WT}$ and dimerization-deficient $KRAS^{D154Q}$ in KRAS-driven murine and human LUAD cell lines lacking the wild-type *KRAS* allele and evaluated the *in vitro* and *in vivo* impact on tumor progression and response to MEK inhibition.

Results: $KRAS^{WT}$ decreased *in vitro* and *in vivo* fitness of human and murine *KRAS* mutant LUAD tumor cells. However, this phenotype was reverted upon MEK inhibition, with *KRAS* LOH cells being more sensitive than $KRAS^{WT}$ expressing cells. Interestingly, both effects were dependent on wild-type/mutant KRAS dimerization and not observed with the dimerization-deficient $KRAS^{D154Q}$. We provide a mechanistic model of the ambivalent function of $KRAS^{WT}$, linking its tumor suppressor function with increased MEK inhibitor resistance through dimerization with mutant KRAS.

Conclusions: • $KRAS^{WT}$ affects cellular fitness in KRAS-driven LUAD • $KRAS^{WT}$ impairs response to MEK inhibitors in KRAS-driven LUAD • $KRAS^{WT}$ inhibitory effect is dependent on dimerization with mutant KRAS • Impaired wild-type/mutant KRAS dimerization restores sensitivity to MEK inhibitors *in vivo*.

Legal entity responsible for the study: Dana Farber Cancer Institute

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2O CDCP1 initiates tumorigenesis and cooperates with PTEN loss to promote senescence evasion and prostate cancer progression

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Background: Elevated levels of CUB domain-containing protein 1 (CDCP1) have been reported to be associated with poor prognosis in several human malignancies, including prostate cancer. However, its oncogenic role remains unexploited. Taking an advantage of multiple cross species genetic models, we demonstrate that CDCP1 *per se* is an oncogene. Particularly in mice, overexpression of CDCP1 in prostatic epithelial cells initiates hyperplasia, which eventually develops high-grade prostatic intraepithelial neoplasia. The functional importance of CDCP1 in tumuorigenesis was further fortified based on the evident display of invasive and metastatic prostate tumors upon its overexpression concomitantly with loss of *Pten* in mouse prostates. Mechanistically, we demonstrate that CDCP1 leads to the activation of SRC that further enhances the level of the transcription factor c-Myc *in vivo*. In turn, enhanced Myc triggers transcriptional activation of *Cyclin D1* and *COUP transcription factor II (COUPTF-II)* that bypasses the TGF-β-dependent checkpoint and senescence barrier driven by *Pten*-loss. Following on, we demonstrate that targeting CDCP1 antagonizes *c-Myc* expression to block tumourigenesis by reactivating cellular senescence in human prostate cancer cells.

Methods: CDCP1, transgenic mouse model, PTEN, prostate cancer.

Results: -Conditional overexpression of CDCP1 promotes tumourigenesis in different transgenic model systems -CDCP1 cooperates with *Pten*-loss in driving full malignant prostate tumourigenesis -Overexpression of CDCP1 overcomes *Pten*- loss induced cellular senescence by activating Myc-Targeting CDCP1 induces cellular senescence and growth arrest by downregulating Myc.

Conclusions: In sum, our findings highlight a crucial role for CDCP1 in 1) driving tumourigeneis in several transgenic models and 2) inducing full malignant progression of *Pten*-null prostate tumourigenesis by eliciting an oncogenic and tumour suppressive network that results in senescence evasion and metastasis. As CDCP1 is a cell surface protein which can be targeted by currently available monoclonal antibodies, our study also put forth a novel therapeutic strategy to target SRC and MYC tumours in metastatic human prostate cancer.

Legal entity responsible for the study: IOR-Bellinzona- Andrea Alimonti

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Disclosure: All authors have declared no conflicts of interest.

3PD New targets in triple negative breast cancer: Role of oncostatin M receptor pathway

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Background: Triple Negative (TN) breast tumours have poor prognosis, lack of targeted therapies and are often refractory to conventional chemotherapy treatments. Therefore, finding new therapeutic targets for those tumours is an unmet need with high clinical impact. In this context, Oncostatin M receptor (OSMR) is a promising therapeutic target as it is over-expressed in this tumour subtype and its activation promotes invasiveness[1,2]. We previously showed that OSMR is frequently copy-number gained and over-expressed in squamous cell carcinoma, where it induces migration, invasion and metastasis[3,4,5]. We now investigate the role of OSMR in breast cancer progression. 1. Guo L, *et al.* (2013) *Oncogene* 32: 5272–5282. 2. West NR, *et al.* (2014) *Oncogene* 33: 1485-1494 3. Caffarel MM, Coleman N. (2014) *Journal of Pathology* 232:386-90 4. Caffarel MM, *et al* (2013) *Journal of Pathology* 231:168-79 5. Kucia-Tran, *et al.* (2016) *Brit J Cancer* 115:212-222.

Methods: To address this issue we use a wide array of tools including *in vitro* cell cultures and *in vivo* models. The expression of OSMR pathway was analysed in FFPE samples and large datasets of publicly available breast cancer samples (METABRIC, n = 1462; and TCGA, n = 547).

Results: OSMR and its ligand Oncostatin M (OSM) are over-expressed in basal tumours, where they associate with shorter overall survival ($p = 0.015$). While OSMR is expressed by breast cancer cells, the main source of OSM seems to be the tumour stroma, primarily cancer associated macrophages and fibroblasts. OSM treatment of breast cancer cells induces the expression of important mediators of angiogenesis and invasion. Importantly, OSMR activation accelerates tumour onset, tumour growth and metastasis in orthotopic xenografts in nude mice.

Conclusions: Our results support that OSMR pathway may have an important role in the initiation and progression of breast cancer and that it could be a promising candidate for therapeutic targeting in Triple Negative Breast Cancer. OSMR could be blocked by antibody based inhibition, strategy that has had a major impact on breast cancer.

Legal entity responsible for the study: Molecular Oncology group, Biodonostia Health Research Institute

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Disclosure: All authors have declared no conflicts of interest.

4PD GGNBP2 suppresses tumor growth and cancer stem cell load of triple negative breast cancer by controlling STAT3 pathway

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Background: Gametogenetin binding protein 2 (GGNBP2) is encoded in human chromosome 17q12-q23, a region known as a breast and ovarian cancer susceptibility locus. GGNBP2 has a single C2H2 zinc finger and a consensus LxxLL nuclear receptor (NR) binding motif. We have reported that GGNBP2 suppresses ERα-positive breast tumorigenesis by acting as a nuclear receptor co-repressor to restrain ERα activity.

However, the detailed molecular mechanisms of GGNBP2 and its role in triple negative breast cancer (TNBC) remain largely unclear.

Methods: A human breast cancer tissue array containing 138 human breast tumor tissues were utilized to examine *GGNBP2* expression in breast cancer samples by IHC. To address the potential anti-breast tumor activity of GGNBP2 *in vitro*, we expressed exogenous *GGNBP2* in TNBC cells, including MDA-MB-231 and Cal51 cell lines. Cell proliferation and cell cycle were assessed by cell growth curve/EdU assays and flow cytometry after propidium Iodide staining. Apoptosis was determined by flow cytometry after annexin V staining, by caspase 3/7 and caspase 9 activity assays. Cancer stem cell properties were determined by expression of CD44/CD24/ALDH1 markers. The levels of phosphorylated STAT3 and total STAT3 were determined by western blot. Quantitative PCR and Western blot were carried out to evaluate the effects of GGNBP2 overexpression on STAT3 target genes, CCND1, Mcl-1, survivin, bax and bim expression.

Results: GGNBP2 expression is down-regulated in TNBC cells and patient tumors and it is associated with poor patient survival. Overexpression of GGNBP2 significanly induces cell cycle G0/G1 phase arrest and apoptosis in TNBC cell lines. Expression of cancer stem cell markers also decreased in GGNBP2-overexpressed TNBC cells. GGNBP2 reduces the expression levels of CCND1, Mcl-1 and survivin, promotes the expression levels of bax and bim proteins. Importantly, overexpression of GGNBP2 inhibits STAT3 phosphorylation and STAT3 downstream garget gene expression, including CCND1, Mcl-1 and survivin.

Conclusions: GGNBP2 serves as a critical nuclear negative regulator of STAT3-mediated gene expression and tumorigenesis.

Legal entity responsible for the study: Jin Zhang

Funding: None

Disclosure: All authors have declared no conflicts of interest.

5PD The acquired resistance to the combination of the anti-EGFR cetuximab and the MEK-inhibitor refametinib in KRAS mutated colorectal cancer cell lines depends on PI3K-signalling

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Background: Previous studies showed that the combination of an anti-epidermal growth factor (EGFR) and a selective MEK-inhibitor displays a significant anti-tumour activity in RAS-wild type colorectal cancers (CRCs), while the same combination partially reverts anti-EGFR primary resistance in KRAS mutated colorectal cancer cell lines. However, mechanisms of resistance to this combination are still unexplored.

Methods: We generated KRAS mutated CRC cell lines (HCT15 and HCT116) resistant to a combination of cetuximab (an anti-EGFR antibody) and BAY86-9766 (refametinib, a selective MEK1/2-inhibitor) after continuous exposure to increasing concentration of the drugs for 8 months. Resistant clones had an IC_{50} 20-100-fold higher than the parental cells. We evaluated by Western Blot (WB) analysis and quantitative Reverse Transcriptase Polymerase Chain Reaction (qRT-PCR) the expression and activation status of a panel of receptor tyrosine kinases (RTKs) and intracellular transducers. We further analysed by MTT assay the sensitivity of these cetuximab-MEKi resistant (CM-res) cell lines to GDC-0941 (pictilisib, a selective PI3Kα inhibitor) and afatinib (BIBW 2992, an irreversible pan-HER inhibitor) either used alone or in combination.

Results: We found consistent hyperactivation of the PI3K-AKT pathway and concurrent inactivation of the MAPK pathway, coupled to the activation of multiple RTKs of the HER family such as HER2 and HER3 in resistant cells when compared to parental cells. Treatment with GDC-0941 was able to partially restore the sensitivity to the drug combination, suggesting a central role for this pathway in mediating resistance in this setting, while afatinib was not capable of reverting the resistant phenotype when used alone but showed synergistic activity when combined to GDC-0941.

Conclusions: These preliminary results suggest that PI3K activation plays a central role in the acquired resistance to the combination of anti-EGFR and MEK-i. PI3K activation depends at least in part by the activation of the HER family of RTK, but it can also be activated by other receptors. In vivo experiments on mice are currently ongoing.

Legal entity responsible for the study: University of Campania "L. Vanvitelli"

Funding: Associazione Italiana per la Ricerca sul Cancro (AIRC)

Disclosure: All authors have declared no conflicts of interest.

6PD FPA150, a novel B7-H4 therapeutic antibody with checkpoint blockade and ADCC activities

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Background: B7-H4, a member of the B7 family of immune modulators, negatively regulates both T cell immune responses and anti-tumor immunity. While B7-H4 is highly expressed in a range of solid tumors, expression in heathy tissues is limited. Hence, we sought to generate a therapeutic antibody that both blocks the T cell inhibitory checkpoint activity of B7-H4 and mediates potent antibody-dependent cell-mediated cytotoxicity (ADCC) against B7-H4-expressing tumor cells.

Methods: Fully human B7-H4 antibodies raised by screening Adimab's yeast-based platform were evaluated for protein and cell binding, epitope specificity, and species cross-reactivity. We assessed these B7-H4 antibodies for checkpoint blockade activity using our proprietary in vitro assay, comprised of primary human T cells and B7-H4-expressing artificial antigen presenting cells. We used primary human cell-based and reporter cell line-based assays to assess the in vitro ADCC activity of B7-H4 antibodies against B7-H4-expressing target cell lines. We assessed the in vivo anti-tumor efficacy of our lead B7-H4 antibody in mice bearing syngeneic tumor cell lines engineered to display mouse B7-H4.

Results: After generating a panel of B7-H4 antibodies, we found that 12 out of 41 antibodies reverse B7-H4-mediated inhibition of T cell proliferation and IFNg production in vitro. Importantly, 11 of these antibodies with checkpoint blockade activity belong to the same epitope bin, recognize the B7-H4 IgV domain, and fully cross-react with cynomolgus monkey and rodent B7-H4, suggesting that these antibodies bind and block an evolutionarily conserved functional domain. When glycoengineered for enhanced FcgRIIIa binding, selected checkpoint blockade antibodies also mediate potent ADCC activity against cells exhibiting a range of B7-H4 expression. In a murine tumor model expressing B7-H4, our selected therapeutic candidate FPA150 significantly impairs tumor growth in a dose-dependent manner.

Conclusions: We generated a therapeutic candidate B7-H4 antibody, FPA150, which possesses both T cell immune checkpoint blockade and ADCC activity. We initiated IND-enabling studies and plan to file an IND application by the end of 2017.

Legal entity responsible for the study: Five Prime Therapeutics

Funding: Five Prime Therapeutics

Disclosure: C.D. Kaplan: Currently employed by and own stock in Five Prime Therapeutics. D. Houser, A. Hsu, K. Legris, G. Brattich, H. Xiang, A. Ahene, U. Jeffry, D. Bellovin, L. Borges, F. Kemp: Currently employed by Five Prime Therapeutics N. Nielson: Currently employed by Adimab.

7P GSKJ4, an H3K27me3 demethylase inhibitor, effectively suppresses the breast cancer stem cells

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Background: Breast cancer stem cells (BCSCs) are responsible for breast cancer metastasis and treatment failure. Hence, eliminating BCSCs poses possibility to eradicate breast cancer. Recently, studies have been suggested that H3K27me3 is implicated in maintenance of cancer stem cells (CSCs), however, the roles of H3K27me3 in BCSCs remain poorly investigated. Hence, we aimed to explore the functionality of H3K27me3 in BCSCs.

Methods: Here, we firstly determined the global level of H3K27me3 in mammosphere-derived cells. Then, we detected the effect of GSKJ4 in cell viability through CCK8 assay. Next, we tested the impact of GSKJ4 on BCSCs expansions with CD44+CD24- phenotype and ALDH1-positive via flowcytometry. In addition, the impact on self-renewal capacity of BCSCs were also asked using mammosphere formation assay and colony formation assay. Further, western blot and Q-PCR were conducted to explore the effect of GSKJ4 in the expression level of stemness-related markers. Finally, we determined the influence of GSKJ4 on tumorigenicity using a xenograft model and investigated the underlying mechanisms.

Results: We identify H3K27me3 as a negative modulator of stemness of BCSCs and suggest GSKJ4 is a promising drug targeting BCSCs. we show that the H3K27me3 level is decreased in mammosphere-derived BCSCs. In breast cancer cells, we demonstrate that GSKJ4 could markedly inhibit the proliferation. Strikingly, we show that GSKJ4 could effectively suppress BCSCs including its expansion, self-renewal capacity, and the expression of stemness-related markers. Additionally, our xenograft model confirms that GSKJ4 is able to effectively inhibit the tumorigenicity of MDA-MB-231. Mechanistically, the inhibition effect of GSKJ4 in BCSCs is via inhibiting JMJD3 and UTX thus causing increment of H3K27me3 level, which results in suppressing stemness factors including NANOG, SOX2 and OCT4.

Conclusions: Our results provide strong supports that epigenetic modification is associated with maintenance of properties of BCSCs and reveal that GSKJ4 is capable to be a prospective agent targeting BCSCs.

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Funding: None

Disclosure: All authors have declared no conflicts of interest.

8P The impact of rotenone-modulated oxidative stress on the survival of human breast cancer stem cells (CD24-/CD44+)

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Background: Cancer stem cells (CSCs) have been proven to be tumorigenic and may be responsible for the resistance to chemo-radiation therapy, disease recurrence and metastasis. Chemo-radiation therapy modulates oxidative stress in cancer cells, leading to cellular adaption response including modulation of cell survival and antioxidant defense mechanisms. However, the redox status alteration of breast CSCs is not yet clearly understood. The aim of this study was to elaborate the impact of rotenone-modulated oxidative stress on the survival of human breast CSCs (CD24-/CD44+) which might be beneficial to understand the underlying mechanism of chemo-radiation therapy resistance.

Methods: Human breast CSCs (CD24-/CD44+) and non-CSCs (CD24-/CD44-) were treated with rotenone and DMSO (vehicle) for 6 hours, respectively. The effects of rotenone on oxidative stress were assessed by analysing intracellular reactive oxygen species (ROS) level using dihydroethidium assay, as well as mRNA expression and specific activity of MnSOD antioxidant. Finally, cell survival was determined using MTS assay, as well as through analysis of survivin mRNA expression.

Results: Our results showed that rotenone could not modulate the superoxide level of human breast CSCs (CD24-/CD44+), in contrast to that of non-CSCs (CD24-/CD44-). Albeit MnSOD synthesis in human breast CSCs has been excessively enhanced following rotenone treatment, the enzyme activity was still lower than in non-CSCs. Importantly, the cell viability of CSCs was higher than that of non-CSCs, which related to the increase of survivin.

Conclusions: We conclude that human breast CSCs (CD24-/CD44+) could survive better than their counterpart non-CSCs (CD24-/CD44-) when treated with rotenone. This impact might be associated with the increase of antioxidant MnSOD expression and survivin mRNA expression.

Legal entity responsible for the study: Faculty of Medicine, Universitas Indonesia

Funding: None

Disclosure: All authors have declared no conflicts of interest.

9P Kynurenine-3-monooxygenase (KMO) protein promotes triple negative breast cancer progression

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Background: Triple-negative breast cancer (TNBC) remains a difficult-to-treat cancer and the biology beneath TNBC is a research interest. Tryptophan-kynurenine metabolism plays an important role in epithelial-mesenchymal transition (EMT), cancer stem cells (CSCs) and immune escape. Previous studies have focused on the expression and function of the first step and the rate-limiting enzyme in tumor cells, whereas the second step catabolic enzyme kynurenine 3-monooxygenase (KMO) was rarely addressed in tumorigenesis. Hence, we sought to investigate of the mechanism and functions of KMO in TNBC carcinogenesis.

Methods: KMO gene alteration and mRNA transcripts were analyzed from the The Cancer Genome Atlas (TCGA) database. MDA-MB-231 and MDA-MB-468 TNBC cell lines were used for *in vitro* studies. Cell proliferation, colony formation, transwell migration/invasion assays and tumorsphere forming ability were used for functional study. Signal transduction pathways were assessed by Western blot, quantitative real-time PCR and reporter assays. The effect of KMO on tumor growth was tested in nude mice with breast cancer xenografts.

Results: TCGA analysis showed high-frequency of KMO amplification alterations, which was related to poor overall survival in breast cancers. KMO transcripts were up-regulated in the tumor tissues of breast cancers, especially in TNBC. The functional assays showed that ectopic KMO expression promoted tumorigenesis, including cell growth and abilities of colony formation, migration, invasion, and tumorsphere formation. Moreover, western blot analysis revealed expressions of epithelial marker E-cadherin were decreased and mesenchymal markers N-cadherin, and Twist were increased by KMO overexpression in MDA-MB-468 cells. Interestingly, the mRNA and protein levels of pluripotency genes including CD44, Nanog, Oct4, and SOX-2 were also suppressed by KMO knockdown. Data of reporter gene assay showed that the activities of Nanog, Oct4, and SOX-2 promoters were enhanced by KMO overexpression. Furthermore, knockdown KMO decreased the xenografted tumor growth of MDA-MB-468 cells, suggesting its oncogenic role in TNBC.

Conclusions: Our data highlight the novel and critical roles of KMO in TNBC progression and metastasis.

Legal entity responsible for the study: Taipei Veterans General Hospital

Funding: Taipei Veterans General Hospital

Disclosure: All authors have declared no conflicts of interest.

10P PIM1 kinase promotes cell migration via SHP2 in triple-negative breast cancer

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Background: Triple-negative breast cancers (TNBCs) are aggressive and associated with poor prognosis. We have recently demonstrated that PIM1 regulates cell death, tumour growth and chemotherapy response in TNBC. This study aims to further explore the molecular mechanisms by which PIM1 promotes malignant phenotypes in TNBC, in particular cell migration.

Methods: The HumanHT-12 v4 expression array was used to interrogate changes in gene expression upon PIM1 knockdown in TNBC cell lines. Transwell migration assays and time-lapse live-cell imaging were used to study the role of PIM1 in cell migration. To assess the morphology of TNBC cells we stained F-actin with 488-phalloidin. Phospho-kinase arrays were used to elucidate the pathway by which PIM1 may control cell migration.

Results: Gene expression analysis revealed PTPN11 as the most downregulated gene upon PIM1 knockdown in TNBC cell lines. These results were validated by qRTPCR in 3 TNBC cell lines. PTPN11 encodes for the phosphatase SHP2, known to be relevant for the migration of TNBC cells. We therefore studied whether PIM1 was also required for this phenotype in TNBC cell lines. PIM1 knockdown led to a defect on 2D-transwell migration in MDA-MB-231 and SUM159 cells, similar to that observed upon SHP2 knockdown. Interestingly, SHP2 knockdown did not affect short-term cell population growth of TNBC cells, suggesting that PIM1 exerts its role in cell population growth via different mechanisms, as demonstrated previously. Upon PIM1 knockdown, MDA-MB-231 showed lower motility persistence, increased circularity and a reduction of F-actin filaments. To understand the common downstream targets of PIM1 and SHP2 and elucidate the pathway by which PIM1 may control cell migration, we used phospho-kinase arrays. These revealed decreased phosphorylation of PLCg1, FAK and PYK2, proteins involved in cell migration, upon either PIM1 or SHP2 knockdown.

Conclusions: These data suggest that PIM1 regulates cell migration by controlling *PTPN11*/SHP2 expression and provide further evidence for PIM1 as a target for TNBC therapy, not only to induce apoptosis and prevent tumour growth, but also to prevent TNBC migration.

Legal entity responsible for the study: King's College London/Breast Cancer Now

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Disclosure: All authors have declared no conflicts of interest.

11P SHP-1 agonist SC-43 enhanced the anti-tumor effect of docetaxel through suppressing p-STAT3 in triple negative breast cancer cells

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Background: Triple negative breast cancer (TNBC) is an aggressive cancer and its prognosis remains poor. Combinational therapies are a promising strategy for enhancing treatment efficacy. Blockade of STAT3 signaling have been shown to enhance the response of cancer cells to conventional chemotherapeutic agents. Here we used a SHP-1 agonist SC-43 to dephosphorylate STAT3, thereby suppressing oncogenic STAT3 signaling, and tested it in combination with docetaxel in TNBC cells.

Methods: TNBC cell lines (HCC-1937, MDA-MB-468, MDA-MB-231) were used for in vitro studies. Cell viability was examined by MTT assay. Combination index was determined using Calcusyn anaysis. Apoptosis was examined by flow cytometry and western blot. Signal transduction pathways in cells were assessed by western blot. In vivo efficacy of SC-43 in combination with docetaxel was tested in nude mice with breast cancer xenografts.

Results: To exam expression of SHP-1 in clinical samples, we analyzed mRNA expression of SHP-1 gene (ptpn6) in a public TNBC dataset (The Cancer Genome Atlas, TCGA). We found that higher SHP-1 mRNA expression is associated with better overall survival in TNBC patients. Sequential combination of docetaxel and SC-43 in vitroshowed enhanced anti-proliferation and apoptosis associated with decreased p-STAT3 and decreased STAT3-downstream effector cyclin D1 in the TNBC cell lines MDA-MB-231, MDA-MB-468 and HCC-1937. Ectopic expression of STAT3 reduced

theincreased cytotoxicity induced by the combination therapy. In addition, this sequential combination showed enhanced SHP-1 activity compared to SC-43 alone. Furthermore, siRNA against SHP-1 reduced apoptosis induced by the combination treatment. Moreover, by ectopic expression of SHP-1 mutants that caused SC-43 to lose its SHP-1 agonist capability, the SC-43-induced p-STAT3 signaling inhibition was reduced in the cells subjected to the combination treatment, suggesting SHP-1 plays a crucial role in docetaxel-SC-43-mediated TNBC cell apoptosis, Importantly, combination of docetaxel and SC-43 showed enhanced anti-tumor growth compared to single-agent therapy in MDA-MB-231 xenografted tumor mice.

Conclusions: SHP-1 agonist SC-43 enhanced the anti-tumor effect of docetaxel by SHP-1 dependent STAT3 inhibition in human TNBC cells. We suggest a therapeutic potential of SHP-1 agonist in combination with docetaxel for TNBC.

Legal entity responsible for the study: National Taiwan University Hospital

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Disclosure: All authors have declared no conflicts of interest.

12P Delineating the mechanisms of resistance to panHER inhibitors in HER2+ breast cancer cells

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Background: Despite the increase in patient survival rates promoted by increased screening and prevention efforts, much faster tumor genome sequencing and developed smart targeted therapies, de novo or acquired chemoresistance remains to be a significant factor for treatment failure in breast cancer therapeutics. Conventional chemotherapy, radiotherapy as well as targeted therapies activate mitochondrial cell death machinery to eliminate cancer cells. BCL-2 protein family members regulate mitochondrial cell death pathway by controlling mitochondrial outer membrane permeabilization. Neratinib and dacomitinib are potent and irreversible pan-EGFR inhibitors, which block their autophosphorylation and downstream signaling. Moreover, neratinib and dacomitinib have been shown to activate cell death in HER2-overexpressing cell lines. The aim of our study was to identify molecular pathways responsible for panHER2 inhibitor resistance in HER2+ breast cancer cells.

Methods: The expression of EGFR and BCL-2 protein family members was determined by immunoblotting and qPCR. CellTiter-Glo was used to measure cell viability and AnnexinV/PI staining and flow cytometer was used to evaluate apoptotic response. BH3 profiling was used to determine the apoptotic blocks and mitochondrial cell death priming in breast cancer cells.

Results: Here we showed that increased MCL-1 and decreased BIM mediate resistance to neratinib in ZR-75-30 and SKBR3 cells while increased BCL-XL and BCL-2 and decreased BIM promoted neratinib resistance in BT474 cells. Cells were also cross-resistant to dacomitinib. BH3 profiles of HER2+ breast cancer cells efficiently predicted anti-apoptotic protein dependence and development of resistance to panHER2 inhibitors. Adding specific ERK1/2 inhibitor SCH772984 to neratinib or dacomitinib led to increased apoptotic response in SKBR3 and ZR-75-30 cells, but we did not detect a similar response in BT-474 cells. Reactivation of ERK1/2 was primarily responsible for acquired resistance in SKBR3 and ZR-75-30 cells. Intriguingly, both ERK1/2 and Akt/NFkappaB pathways were responsible for neratinib resistance in BT474 cells.

Conclusions: Our results showed that different mitochondrial apoptotic blocks mediated acquired panHER2 resistance in HER2+ breast cancer cell lines as well as highlighted the potential of BH3 profiling assay in prediction of panHER2 resistance in breast cancer cells.

Legal entity responsible for the study: Ozgur Kutuk

Funding: Baskent University

Disclosure: All authors have declared no conflicts of interest.

13P AXL as a potential primary and secondary trastuzumab resistance mechanism in breast cancer cells with HER2 overexpression

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Background: Breast cancer (BC) is a heterogeneous disease, HER2+ represents between 15-30% of all subtypes. Trastuzumab (T), a monoclonal antibody able to inhibit HER2 activation, has been successfully employed in HER2 amplified tumors both in adjuvant and in metastatic settings, conferring an improvement in DFS, PFS and OS. Despite these results, many patients experience primary or secondary resistance to therapy. The mechanism of resistance is unclear, our aim is to assess AXL, a receptor tyrosine kinases (RTK) implicated in epithelial-to-mesenchymal transition, as potential mechanisms of resistance.

Methods: We used two cell lines to investigate possible mechanisms of primary and secondary resistance to T in HER2+ and hormone receptor negative BC. AU565 sensitive to T (AU565-S), and HCC1954 a primary T-resistant cell line. A third cell line with acquired resistance to T (AU565-R) was generated by treating AU565-S cells with constant dose of T (15mg/mL) for 4 months. Cell viability was estimated by MTT assay. We explored the expression of AXL by Western blot (WB) and quantitative reverse transcriptase PCR (qRT-PCR).

Results: The cell viability analysis at 7 days assay confirmed AU565-S as sensible to T, HCC1954 as primary resistant and the development of a secondary resistance to T (AU565-R) (50% of increased viability from AU565-S). HER2 overexpression in all three cells lines were confirmed by WB and FISH. qRT-PCR indicated an important up-regulation of AXL at mRNA levels in AU565-R and HCC1954 compared to AU565-S ($p < 0.05$). In the same line, WB analyses showed a significantly increase in AXL protein expression in AU565-R and HCC1954 (2.03 and 7.37 fold, respectively). Finally, a selective AXL inhibitor (TP-0903) has demonstrated reduction of viability in all cell lines and significant restoration of sensitivity to T in AU565-R ($p < 0.01$).

Conclusions: Our results suggest: 1) AXL could be a potential mechanism of both primary and secondary resistance to T; 2) combination therapy with AXL inhibitor plus T restored T sensitivity in in vitro model with AXL overexpressed. These results merit further study and to explore this RTK as possible therapeutic targets in case of anti-HER2 treatment failure.

Legal entity responsible for the study: Hospital Clinico Universitario of Valencia. Biomedical Research Institute INCLIVA

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Disclosure: J.A. Perez Fidalgo: Received fees from AstraZeneca, Ipsen, Novartis, Pfizer and Roche for participation in speaker bureaus. Had travel/accomodation expenses paid/reimbursed by AstraZeneca, Roche and Sandoz. All other authors have declared no conflicts of interest.

14P Alterations to trastuzumab-induced antibody-dependent cell-mediated cytotoxicity (T-ADCC) in a lapatinib-resistant HER2+ breast cancer cell line model

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Background: Lapatinib is a dual targeting (EGFR/HER2) small molecule tyrosine kinase inhibitor (TKI) approved for the treatment of HER2+ breast cancer. Lapatinib treatment can often lead to acquired resistance and refractory disease. There is no data available on the sensitivity of lapatinib-resistant breast cancer cells to immune cell-mediated cytotoxicity. To investigate the consequences of a lapatinib resistant phenotype on the immune response, we examined T-ADCC and the expression levels of immune-related proteins in a cell line model of lapatinib-resistant HER2+ breast cancer.

Methods: Lapatinib-resistant SKBR3 cells (SKBR3-Lap) were generated by continuous exposure to 250nM lapatinib for 6 months alongside untreated parental cells (SKBR3-Par). FACS-based assays employing peripheral blood mononuclear cells (PBMCs) isolated from healthy volunteers were used to measure direct PBMC-mediated cytotoxicity and T-ADCC. Comparative DNA microarray studies (SK-Par vs. SK-LAP) identified differentially expressed immune-related genes which were subsequently examined at the protein level by Western blot.

Results: T-ADCC was 45-50% lower in SKBR3-Lap compared to the SKBR3-Par cell line at the three effector to target cell ratios examined - 1:1 ($p = 0.01$), 5:1 ($p = 0.001$) and 10:1 ($p = 0.024$). Direct immune cell-mediated cytotoxicity was low (<7% at 10:1) for both cell lines. Microarray data identified significant alterations in the growth factor receptor EGFR, the immunosuppressive adenosine receptor A2AR and immune response modulating MHC Class I, HLA-E, and NKTR in SK-LAP compared to SK-Par. Western blots established changes to these targets at the protein level. In addition, protein levels of HER2 were not significantly reduced and programmed death ligand 1 (PD-L1) levels were increased ($p = 0.045$) in SKBR3-Lap.

Conclusions: Resistance to lapatinib is associated with an attenuated T- ADCC response and an altered profile of immune-related proteins in this HER2+ breast cancer model. Further investigation is warranted to explore if targeting proteins such as A2AR or PD-L1 could play a role in ADCC response in this model.

Legal entity responsible for the study: Cancer Biotherapeutics, National Institute for Cellular Biotechnology, Dublin City University

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15P Estrogen-dependent breast cancer: The importance of androgen receptor in exemestane treatment

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Background: Exemestane (Exe) is a third-generation steroidal aromatase inhibitor (AI) that is a standard therapeutic approach for post-menopausal women with estrogen-receptor positive (ER+) breast cancer. Besides its clinical benefit, acquired resistance may develop. Thus, to avoid this drawback it is urgent to find new targets that can improve breast cancer treatment. It is known that 85-95% of the ER+ breast cancers, overexpress androgen receptor (AR), that has a dual function in breast cancer depending on hormonal cell status. It has been described that in AIs-sensitive breast cancer cells this receptor promotes cell death. Several clinical trials are ongoing to study the efficacy of combining AR antagonists, as bicalutamide (CDX), with Exe, but the benefit of targeting AR is not well defined. In that way, this work will investigate the biological significance of AR in Exe-treated breast cancer cells and the effectiveness of targeting AR.

Methods: In ER+ breast cancer cells that overexpress aromatase (MCF-7aro), it was investigated the in vitro effects of the AR antagonist CDX in Exe-treated cells. The cell impact in viability and cell proliferation was studied using MTT assay and flow cytometry, respectively. The cell death was explored by evaluating caspase activities. The expression/activation of AR and the effects on PI3K and MAPK pathways were studied by Western-blot.

Results: Exe induces an overexpression and hyperactivation of AR in MCF-7aro cells. By blocking AR with CDX, it was observed an increase in the reduction of viability and proliferation of Exe-treated cells, when comparing to Exe alone. An increase in activation of caspases-9, -8 and -7 was also observed for the combination. In addition, CDX inhibits the Exe-induced activation of cell proliferation/survival MAPK pathway and caused no effect on PI3K pathway.

Conclusions: This study suggests that, contrary what is described for other AIs, the AR as a pro-survival role in sensitive breast cancer cells treated with Exe and that by targeting AR it is possible to improve the clinical efficacy of Exe, by inhibiting cell proliferation and inducing apoptosis. This work contributes to the understanding of the link between AR and Exe and will highlight new targets to improve breast cancer treatment.

Legal entity responsible for the study: UCIBIO, REQUIMTE, Faculty of Pharmacy, University of Porto

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16P Phosphatidylinositol 3-kinase (PI3Kα)/AKT axis blockade with taselisib or ipatasertib enhances the efficacy of anti-microtubule drugs in human breast cancer cells

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Background: The phosphatidylinositol 3-kinase (PI3Ks) pathway is commonly altered in breast cancer patients, but its role is still unclear. Taselisib, a mutant PI3Kα selective inhibitor, and ipatasertib, an AKT inhibitor, are currently under investigation in clinical trials in combination with paclitaxel or hormonal therapies in breast cancer. The aim of this study was to evaluate if PI3K or AKT inhibition can prevent resistance to chemotherapy and potentiate its efficacy.

Methods: The efficacy of combined treatment of ipatasertib and taselisib plus vinorelbine or paclitaxel or eribulin was evaluated in vitro on human breast cancer cells (with different expression profile of hormonal receptors, HER2, and of PI3Kα mutation) on cell survival by using MTT (3,(4,5-dimethylthiazol-2)2,5 difeniltetrazolium bromide) and on cell apoptosis by flow-cytometry analysis. We also investigated the effect of combined treatment on downstream intracellular signaling, by western blot analysis, and on metastatic properties, by migration assays. Finally, we analyzed changes in cell cytoskeleton by immunofluorescence.

Results: A significant synergism of ipatasertib or taselib plus anti-microtubule chemotherapy in terms of anti-proliferative, pro-apoptotic and anti-metastatic effect was observed. The combined treatment completely inhibited the activation of proteins downstream of PI3K and MAPK pathways and affected the expression of survivin. Combined treatments completely disorganized the cytoskeleton in human breast cancer cells, thus suggesting a potential mechanism for this combination.

Conclusions: Targeting PI3K may enhance the efficacy of anti-microtubule drugs in human breast cancer.

Legal entity responsible for the study: Università degli Studi della Campania "Luigi Vanvitelli", Naples, Italy.

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18P Potential miRNAs involved in molecular pathways mediating the anticancer effects of short term starvation in breast cancer cells treated with doxorubicin

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Background: In recent years, increasing evidences showed that several types of dietary approaches restricting food intake, including Short Term Starvation (STS), may exert a protective role against aging and other age-related pathologies as well as cancer. Interestingly, the dietary restriction showed significant anticancer effects able to prevent cancer onset, slow its progression and improve therapy response. Since recent studies showed that miRNAs may modulate sensibility/resistance to antiblastic therapy, the aim of our study was to investigate the STS-induced molecular changes in breast cancer cells treated with doxorubicin, focusing our attention on miRNA expression profile.

Methods: Vitality assays were used to assess the effects of STS on cell proliferation. Using a TaqMan Low Density Array A human microRNA microarray analysis, the expression profile of 377 miRNAs was analyzed in healthy and malignant breast cells, MCF10A and MDA-MB-231 respectively, treated for 24h with 1μM doxorubicin under STS conditions for 48h. In addition, the expression of mRNAs and miRNAs specifically induced by STS was analyzed in MCF-7, MDA-MB-231 and SkBr3 cells using Real-time PCR analyses.

Results: *In vitro* cell vitality assays showed that STS, in association with doxorubicin treatment, significantly reduces breast cancer cell proliferation and viability, whereas it appears to protect healthy breast cells from chemotherapeutic treatment. Microarray analysis showed that a subset of miRNAs involved in molecular pathways related to drug sensitivity/resistance was found to be differentially expressed in breast cancer cells following the doxorubicin treatment and STS. Finally, expression analysis of hypothetical miRNA gene targets involved in therapy response have confirmed the coherence of our results.

Conclusions: This work establishes, for the first time, an interesting link between anticancer effects of STS and miRNA expression changes in doxorubicin-treated breast cancer cells, suggesting the potential involvement of some miRNAs in molecular pathways mediating the effects of STS in breast cancer.

Legal entity responsible for the study: Department of Surgical, Oncological and Oral Sciences, Section of Medical Oncology, University of Palermo

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Disclosure: All authors have declared no conflicts of interest.

19P An endothelial premetastatic-like niche is promoted by tumor-secreted factors derived from highly metastatic breast cancer cells in vitro

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Background: It is well established that primary tumour can modify secondary organs long before the circulating tumor cells reach their metastatic targets. These modifications are mainly exerted through tumor-secreted factors and can act on several cell types to form what is called the pre-metastatic niche. Pre-metastatic endothelial niche play a key role in the extravasation process during metastasis. Here we describe the effect of the mixture of secreted factors by tumor cells over endothelial changes that facilitates tumor cell transendothelial migration.

Methods: Adhesion assay Human umbilical vein endothelial cells (HUVEC) cells were stimulated or not with TNF-α [10ng/ml] or Tumor Secreted Factors (TSFs) [10 μg/ml] from MDA-MB-231 or MCF-7 cell lines. HUVEC monolayers were co-cultured with a U937(^{3}H) cells. After 3h firm attached U937(^{3}H) were lysed and radioactivity was measured. Vascular permeability assay HUVEC monolayers were cultured in Boyden chambers. Cells were stimulated or not with TNF-α [10ng/ml] or TSFs [10 μg/ml] and incubated for 12h. Afterwards a dextran-FITC solution was added for 20 min and the bottom well fluorescence was quantified. Transendothelial migration assay HUVEC monolayers were cultured in Boyden chambers. Cells were stimulated or not with TNF-α [10ng/ml] or TSFs [10 μg/ml] and incubated for 10h. Fluorescent labeled MDA-MB-231 cell suspension 2x10^4 was added (24h) and the migrant cells were counted under an epifluorescence microscope.

Results: Adhesion assay revealed that HUVEC stimulated with MDA-231 TSFs attached U937 cells 6-fold comparing to the MCF-7 TSFs or control, in a similar way as

TNF-α did. The MDA-TSFs were able to increase the HUVEC monolayer permeability exceeded about 30% of the TNF-α induced permeability. A 1.5-fold increase of transendothelial migration cells was observed in HUVEC stimulated with MDA-MB-231 TSFs.

Conclusions: Tumor secreted factors derived from highly metastatic cell line MDA-MB-231 are capable to induce a premetastatic-like endothelial state, increasing the tumor cell transendothelial migration, adhesion to the HUVEC monolayer as well as vascular permeability enhancement.

Clinical trial identification: 11-62-2014

Legal entity responsible for the study: Instituto de Investigaciones Biomédicas, UNAM

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Disclosure: All authors have declared no conflicts of interest.

20P Selective accumulation of the rat adherent natural killer cells in mammary tumor tissues

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Background: In the present study, we attempted to clarify what kind of adhesion molecules and tumor cytotoxic killer activity A-NK cells can express, when cultured for long period in vitro, and then tried experimentally to augment the selective accumulation the A-NK cells into rat mammary tumors, in combination with the prior injection of various kinds of adjuvants into the tumor region. The mechanisms by which the effector cells accumulate in tumor tissue will be discussed.

Methods: 1. Animals: Specific pathogen-free (SPF) female rats. 2. Preparation of A-NK cells: A-NK cells were isolated from splenic lymphocytes. 3. Antibodies: Monoclonal antibodies, and Anti adhesion molecule antibodies. 4. Immunohistochemical staining and Flow cytometric analysis. 5. Preparation of mammary tumor bearing rats.

Results: Immunocytochemical and flow-cytometric analysis revealed that most of the A-NK cells strongly expressed lymphocyte-function-associated antigen 1 throughout the incubation. All A-NK cells from 8-150-day cultures, particularly those cultured for 8 days, showed significant cytolytic activity against all targets. Peritumoral injection of various kinds of adjuvant, particularly Freund's complete adjuvant plus bacillus Calmetee-Guerin, resulted in a marked accumulation of A-NK cells in mammary tumor tissues 24 h after injection, and simultaneously in the formation of vessels resembling high-endothelium venules, and expression of the ICAM-1 molecule on the tumor cells in the sites of tumor tissues. When A-NK cells were intravenously administered, significant retardation of tumor growth and prolongation of survival of tumor-bearing rats were observed in the groups that received the prior injection of adjuvants.

Conclusions: These results indicate that the prior injection of proper adjuvant into the peritumoral region is effective for the selective accumulation or infiltration of A-NK cells into the sites of tumor tissues, and results in the marked retardation of tumor growth.

Legal entity responsible for the study: School of Rehabilitation Sciences

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Disclosure: The author has declared no conflicts of interest.

21P Inhibition of nitric oxide synthase (NOS) reduces the effect of stress hormone signalling in breast cancer

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Background: Expression of nitric oxide synthase (NOS) has been found to correlate with tumour progression in breast cancer, indicating that NO activity may drive malignant growth. Previously we have shown that the stress hormone cortisol acts through a nitric oxide synthase (NOS) mediated pathway to induce production of nitric oxide (NO), and can induce DNA damage in breast cancer.

Methods: Breast cancer cell lines MCF-7 and MDA-MB-231 as well as the mouse mammary tumour cell line 66CL4 were exposed to cortisol and levels of intracellular NO were measured using composite electrochemical sensors. DNA damage was quantified using immunofluorescence and expression of iNOS and metastatic markers VEGF and TWIST were examined using qPCR. An *in vivo* syngeneic breast cancer model was also used to examine the effect of L-NAME, a NOS inhibitor, on tumour aggressiveness and metastasis in conjunction with daily restraint stress (2hrs) (n = 4/group, repeated in duplicate).

Results: Cortisol significantly increased the expression of iNOS, the generation of NO and DNA damage in breast cancer cells and this was blocked by the NOS inhibitor L-NAME. A significant increase in VEGF and TWIST expression was also observed in response to cortisol. Furthermore, L-NAME also significantly reduced primary tumour growth in stressed mice and reduced the number of metastatic sites/mouse. Tumour microvasculature (as evidenced by CD31 expression) was significantly increased in stressed mice and this was reduced with L-NAME treatment.

Conclusions: We demonstrated that L-NAME, through inhibition of NO signalling, is effective in reducing primary tumour formation and metastatic potential in stressed mice. This data may have impact for patients with breast cancer experiencing extreme stress and further genomic analysis are ongoing.

Legal entity responsible for the study: School of Pharmacy and Biomolecular Sciences, University of Brighton, UK

Funding: Rising star initiative, University of Brighton.

Disclosure: All authors have declared no conflicts of interest.

22P The interplay between TP53 and mevalonate pathway in ovarian cancer

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Background: TP53 gene is the most commonly mutated tumour suppressor in human malignancies. TP53 is mutated in more than 50% of all human cancers, with over 96% of high-grade serous ovarian cancer displaying changes at this locus. Mutations of TP53 gene is associated with malignant transformation and resistance to chemotherapy. In addition, previous studies have shown that ectopic expression of TP53 mutant form in breast cancer cells leads to increased transcription of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR). This enzyme regulates the synthesis of geranylgeraniol which is used to post-translationally modify small GTPase oncogenes. HMGCR is itself considered to be a metabolic oncogene. Statins, which inhibit HMGCR, are potential cancer therapeutics which can cause ovarian cancer (OC) cell apoptosis and regression of xenografts.

Methods: The level of mevalonate pathway (MP) enzymes evaluated in panel of OC cell lines using immunoblotting. in addition, MP enzymes expression were evaluate using qPCR following ectopic expression of wild-type and R248W, R175H, and R273H p53 variants in Skov-3 cells and after inhibition of TP53 expression using siRNA directed to TP53 mRNA in Ovcar-3 cells.

Results: We confirmed that the expression of HMGCR is higher in OC cell lines than in normal epithelial ovarian cells. The level of geranylgeranyl transferase I-β (GGTI-β) and Geranylgeranyl transferase II-β (GGTII-β) was significantly higher in a subset of OC cell lines. The ectopic expression of TP53 variants in Skov-3 cells, which lack endogenous p53 protein, led to significantly increased expression of HMGCR, GGTI-β, GGTII-β and Farnesyltransferase-β (FT-β) enzymes compared to cells transfected with vector. The inhibition of the pre-existing mutations in TP53 encoding R248Q in Ovcar-3 cell line significantly decreased p53 protein and also HMGCR, GGTI-β, GGTII-β and FT-β mRNA.

Conclusions: These data suggest that TP53 mutations play critical role in regulation of the activity of MP enzymes, providing a rationale for the evaluation of the pathway inhibitors such as statins and bisphosphonates in the treatment of OC.

Legal entity responsible for the study: The study was designed by AR and MIA, the experimental work was conducted by MIA and MNA.

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Disclosure: All authors have declared no conflicts of interest.

23P Epigenomic landscape of breast cancer in very young women

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Background: Although less frequent than in older women, breast cancer in very young women (BCVY) (≤35 years old) presents more aggressive and complex biological features. Epigenetic modifications such as miRNA regulation or DNA methylation are reported to play an important role in the onset and progression of cancer. The aim of this work is to identify the epigenetics mechanisms characteristics of BCVY that may be conferring more aggressive features to this group of patients.

Methods: We analysed methylation (Infinium MethylationEPIC BeadChip) from 26 BCVY and 15 samples from women >45 years old. Methylation differences were assessed using Wilcoxon rank sum test. We selected from The Cancer Genome Atlas (TCGA) those genes regulated by significantly different methylated sites and their expression was analysed. MiRNA expression data from TCGA, METABRIC and data previously published from our group was evaluated in a meta-analysis. We then selected those target genes which expression was more affected by miRNA deregulation. Pathway enrichment analysis was performed with most relevant genes from the epigenetic study by Enrichr.

Results: We detected a global hypomethylation profile in BCVY samples and hypermetilation of 502 specific CpG sites exclusive of this group of age. Hypomethylated CpG sites were regulating genes mainly involve in neuronal processes, extracellular matrix and cell communication. Whereas specific hypermethylation was located in genes related to immune system, NOTCH signalling, vesicular trafficking, DNA repair and senescence. MiRNA expression meta-analysis revealed a profile of 22 miRNAs significantly deregulated in BCVY. Pathway enrichment analysis of most affected target genes showed an involvement in neural processes, glucose metabolism, vesicular trafficking,

DNA repair, histone and chromatin related proteins, apoptosis, cell cycle, response to DNA damage and senescence.

Conclusions: Our work highlights the presence of epigenomic profile distinctive of BCVY. Both methylation and miRNAs studies points to deregulation of pathways related to neural processes, vesicular trafficking, DNA repair and senescence. All these processes may lead to cancer development and progression, thus genes in these pathways may be potential candidates for further studies.

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24P Evaluation of cell free circulating DNA in plasma by digital PCR for early diagnosis in Peruvian breast cancer patients

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Background: New diagnostic tools can be useful and give clinical benefits, including diagnosis, prognosis, treatment and monitoring of the disease. A new non-invasive method is the study of liquid biopsies, performed in fluids containing cell-free circulating DNA (cfDNA). Analyses with digital PCR technique (dPCR) allows to establish the levels of cfDNA as well as the absolute quantification of mutant alleles with accuracy. This system scatters the sample among twenty thousand wells (microfluids on the chip), where amplification reactions occur independently and are recorded by a reader.

Methods: Peripheral blood samples were obtained from breast cancer patients and healthy controls. From each sample, the cfDNAs were extracted from plasma using the MagMAX™ Cell Free DNA Isolation Kit and dPCR was done for quantification of samples. We evaluated two genes, *PUM1* and *RNaseP*. For amplification of fragments, master mix 1X (Applied Biosystems) and PCR detection assays of both genes were combined with 1.5 µl of plasma cfDNA, dispersed in the chips and placed in a ProFlex ™ thermocycler (Applied Biosystems) following the program pre-established by the manufacturer, with additional five cycles. Finally, quantification data were obtained with QuantStudio® 3D AnalysisSuite™ Cloud Software. Comparison of DNA concentration in copies per microliter and other statistical calculations were performed with InfoStat 2015.

Results: Significant differences were found in the values of cfDNA between patients and controls for PUM1 ($p = 0.0001$) and RNase P ($p = 0.0003$). These results allowed to establish cut-off points between groups at 78,995 and 51,154 copies/uL, respectively. These values can be considered in the classification of groups for further analysis of others samples. Statistical support for the use of markers in diagnosis was also evaluated using the ROC curve that favors the PUM1 marker, with a sensitivity of 75% and a specificity of 95.2%.

Conclusions: Based on the significant differences found between breast cancer patients and controls, cell free DNA is a good biomarker that can be used in the diagnostic of breast cancer. On the other hand, digital PCR has been established as a good tool to check cfDNA levels from plasma of breast cancer patients.

Legal entity responsible for the study: Jose Buleje

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25P Breast cancer predisposing germline mutations identified by exome sequencing

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Background: A significant portion of hereditary predisposition to breast cancer (BC) is attributed to yet unknown factors. Russian population is characterized by surprisingly strong founder effect, therefore whole exome sequencing (WES) for a limited number of these genetically homogenous patients has a potential to identify novel BC-predisposing genes.

Methods: WES was performed for 32 Russian BC cases, which demonstrated strong clinical signs of the hereditary disease (family history, BC bilaterality, young onset) and lacked germline mutations in "canonical" BC genes (*BRCA1, BRCA2, CHEK2, PALB2,* and *NBS1/NBN*).

Results: Eight patients carried potentially pathogenic mutations in BRCA1 network genes (3 truncations (*BLM p.Q548*, RAD51C c.904 + 1G>A, FANCM p.S497fs)* and 5 missense mutations (*FANCM (p.R100W, p.Q891P), ERCC4 p.R799W, RAD54L p.R394W, RAD50 p.D515G)).* The remaining 24 patients were analyzed for the presence of rare non-silent genetic variants; in total, 15437 alleles had ExAC frequency <1%. Use of ACMG-guided bioinformatic pipeline classified these variants for 64 'pathogenic/likely-pathogenic', 12844 of 'uncertain significance', and 2529 'benign/likely-benign'. Prevalence of 69 top candidates was compared in 640 genetically enriched BC patients, 1200 consecutive BC, 1200 middle-aged healthy females and 460 elderly healthy women. Several likely pathogenic mutations were overrepresented in the BC groups: nonsense *PZP p.R680** [9/1845, OR = 13.2]; heterozygous missense *LEPREL1 p.P636S* [6/1778; OR = 4.4] and *ING1 p.P319L* [3/1792; OR = 3.9]; homozygous missense *BRCA1 p.Q356R* [12/1683; OR = 5.5] and *EXO1 p.G759E* [9/1606, OR = 4.3]. Some potentially pathogenic variants occurred only in the index cases but were absent in other BC patients (rare ExAC alleles: *HELLS p.R53C* and *TP53INP1 p.E27D*; newly identified variations: *MLH3 p.C1393F*, *EMSY p.G934** and *ATRIP p.R760**).

Conclusions: This study revealed several alleles, which may be associated with increased BC predisposition. However, in contrast to well-known Slavic BRCA founder mutations, newly identified candidates are exceptionally rare and therefore are unlikely to be responsible for a significant share of BC morbidity. Supported by the RSF grant No 16-45-02011

Legal entity responsible for the study: Evgeny N. Imyanitov, Head of the Department of Tumor Biology in the N.N. Petrov Institute of Oncology

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26P Global transcriptome deregulation of breast cancer in very young women samples

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Background: Breast cancer in young women (under 35 years) (BCVY) often presents distinct clinic-pathological features: more aggressive phenotype and worse prognosis than older women. Genomic and molecular alterations play a significant role in breast cancer biology. Due to the low incidence of BCVY (2-5%) these women are underrepresented in most molecular studies. This work presents a comprehensive study of the transcriptome in BCVY, focusing in the search of gene expression biomarkers characteristic of this group of patients.

Methods: We analysed the transcriptome by Clariom™ D (Affymetrix) from 31 BCVY and 11 samples from women >45 years old. Global gene expression was filtered and normalized by RMA method. After initial pre-processing we analysed expression in 3,639 mRNAs, 66,457 lncRNA and 3,271 pre-miRNA and differences were assessed using t-test. We performed a meta-analysis with gene expression data from The Cancer Genome Atlas (TCGA) for validation of results. Pathway enrichment analysis was performed by Enrichr.

Results: showed a specific transcriptomic landscape in BCVY. Clariom D study revealed 134 significant mRNA with p-value< 0.05 that pointed out towards pathways related with olfactory receptors, GPCR signalling, tight junction and cell-cell communication. After meta-analysis with TCGA gene expression data and own data, 43 genes were statistically significant and 15 of those withstood FDR correction (FDR< 0.05). Among those we found PIK3CB, HOXD10, ZNF654, TMEM204, IRX5, PF4, MAGEA2 and TSR2 deregulated in BCVY compared with older women. Pathway enrichment analyses and GO search highlight pathways related to cell-cell communication, cancer processes, chemokine and PI3K signalling pathways, cell differentiation, extracellular matrix, vesicular trafficking, neuronal processes among others.

Conclusions: We find the presence of a distinctive transcriptomic profile of the BCVY samples. Our study points to deregulation of pathways related to cell migration, proliferation and differentiation that promote cancer development and progression. Genes obtained in meta-analyse might be potential target genes for further studies in BCVY which could help to clarify the biological background for the development of the disease in this group of age.

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27P Integrated system-level analyses of androgen receptor variant networks to identify novel prostate cancer-relevant genes that serve as prognostic biomarkers

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Background: Castration resistant prostate cancer (CRPC) is a rapidly progressing disease state for which there is no cure. The constitutively active androgen receptor (AR) splice variant AR-V7 represents a well-established mechanism of therapeutic resistance and disease progression. This variant lacks the AR C-terminal ligand binding domain and, as such, is not inhibited by androgen deprivation therapy. Designing high-affinity drugs to target the amino terminus of AR and AR-V7 is a major challenge due to the intrinsic disorganized structure of this region. Thus, there is an imperative need to identify novel AR-V7 hub genes in PC that may serve as novel therapeutic targets.

Methods: We performed a highly robust gene expression meta-analysis on PC patient samples. We defined gene modules correlated with PC progression using a Weighted Gene-Co-expression Network Analysis (WGCNA), a powerful systems biology approach. Further, we identified AR-V7 downstream target genes using gene expression profiling and mapped the AR-V7 functional interactome for the first time using a novel high-throughput synthetic genetic array screen in yeast. Finally, we combined the results from our three independent system-level analyses with experimental data to identify hub genes that were upregulated in PC patients, upregulated by AR-V7, and that also functionally interacted with AR-V7.

Results: The identified genes not only included select genes previously linked to PC, such as members of the topoisomerase and cyclin families, but also novel genes that had not been previously linked to PC progression. The identified gene-signature expression correlated with patients' Gleason score and had a prognostic value that predicted disease free-survival at the time of patient biopsy in large independent cohorts.

Conclusions: In sum, we show here an unbiased integrated system-level analysis of AR-V7 networks, where we combined bioinformatic analysis of patient samples and cell-based approaches to identify new candidate genes in CRPC that may serve as novel prognostic markers and future targeted therapies.

Legal entity responsible for the study: University of Miami Miller School of Medicine

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28P ODM-208, a novel CYP11A1-inhibitor as a therapeutic approach for the treatment of castration-resistant prostate cancer

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Background: Androgen receptor (AR) plays a central role in prostate cancer and continues to be a driver in castration-resistant prostate cancer (CRPC), with increased AR expression in most cases. Approximately half of the men with CRPC respond initially to abiraterone or enzalutamide, but most relapse within 1 to 2 years. Majority of the abiraterone and enzalutamide-resistant tumors have still high AR expression and persistent AR activity. Several precursor steroids, like testosterone (T) and dihydrotestosterone activate AR, are synthesized in adrenal glands and de novo in tumours. CYP11A1 (cytochrome p450scc) is a mitochondrial enzyme catalysing the conversion of cholesterol to pregnenolone (Preg), which is the first rate-liming step in steroid hormone biosynthesis. ODM-208 is a novel, oral, non-steroidal and selective inhibitor of CYP11A1 enzyme and suppresses the synthesis of all steroid hormones and precursors.

Methods: The inhibition of CYP11A1 was measured in vitro by detecting the formation of radiolabelled isocapronic acid in a human adrenal cortex cell line (H295R), and further analysing Preg and T formation by ELISA. Inhibition of the adrenal and testicular hormone production in vivo was tested in the intact male rat assay by analysing plasma concentrations of progesterone (P), corticosterone (C) and T (with LS-MS/MS) after single oral dose of ODM-208. The tumor growth inhibition was studied by using androgen dependent VCaP cells, which were subcutaneously grafted to intact male nude mice. When tumor volumes reached on average 200 mm3, mice were castrated, and after regrowth of the tumors, the oral treatment of ODM-208 was started.

Results: ODM-208 potently inhibits CYP11A1 enzyme and formation of Preg and testosterone with low nM concentrations in vitro. In male rats, clear decreases of P, C and T concentrations can be detected already after single oral administration of ODM-208. In the murine VCaP CRPC xenograft model ODM-208 significantly inhibited tumor growth.

Conclusions: ODM-208 shows promising antitumor activity in preclinical CRPC models and suggests that ODM-208 may have the potential to be an effective treatment in CRPC. Clinical trial in patients with metastatic CRPC is planned to be started in the 2018.

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

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Disclosure: R. Oksala, M. Karimaa, M. Ramela, R. Riikonen, P. Rummakko, G. Wohlfahrt, A. Vuorela, M.V. Mustonen, P. Kallio: Employee: Orion Corporation Orion Pharma. All other authors have declared no conflicts of interest.

29P Determining the role of the ETS factor ELF3 in normal and malignant prostate

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Background: Aberrations in the ETS transcription factor family members are a common feature of multiple cancers including prostate cancer (PCa), such as the TMPRSS2:ERG fusion. ELF3, also known as ESE-1, is an epithelial-specific ETS transcription factor involved in regulating cell differentiation in various tissues, however, its role in the prostate is controversial. The aim of this study was to identify the function of ELF3 in normal prostate development and to explore its role in PCa.

Methods: Three model systems were used: prostate cell lines, primary prostate epithelial cells cultured from patient tissue and paraffin-embedded human tissue sections. The function of ELF3 was investigated using knockdown via siRNA transfection and overexpression via lentivirus transduction. Western blots, immunofluorescence and immunohistochemistry were used to measure protein localisation and levels of expression. Other assays measured cell viability, colony forming ability and migration.

Results: ELF3 expression was restricted to the basal layer of the normal prostate epithelium and was not expressed in stroma. Analysis of a prostate tissue microarray indicated that whilst ELF3 is expressed in benign prostate tissue, its expression is lost in low-grade prostate tumours and re-expressed in some more advanced tumours. ELF3 knockdown resulted in decreased migration, cell viability and did not induce stem cell characteristics, whilst promoting basal cell gene expression. ELF3 overexpression increased cell migration. ELF3 was induced in primary prostate epithelial cells following treatment with the clinically approved HDAC inhibitor Vorinostat, which can promote neuroendocrine differentiation.

Conclusions: ELF3 expression correlates with the normal prostate epithelial cell differentiation hierarchy, and may have a role in advanced PCa. Analysis of total gene expression following knockdown of ELF3 will give an indication of transcriptional networks that are regulated by ELF3. In addition, a lentivirus that expresses an ELF3 mutant, which alters its localisation, will be used to assess any cytoplasmic function of ELF3. This comprehensive and clinically relevant approach will allow complete elucidation of the role of ELF3 in prostate cell differentiation and PCa.

Legal entity responsible for the study: Norman Maitland

Funding: Prostate Cancer UK (PCUK) registered charity

Disclosure: All authors have declared no conflicts of interest.

30P Treatment-induced hypoxia attenuates enzalutamide response and promotes resistance in pre-clinical models of prostate cancer

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Background: Inhibition of androgen signalling remains the therapeutic mainstay in castrate-resistant prostate cancer. Retention of active AR signalling or acquisition of splice variants have been reported as mechanisms of resistance to the anti-androgen Enzalutamide. Other non-AR dependent mechanisms of resistance have also emerged including acquisition of a hypoxic microenvironment. We propose treatment-induced hypoxia and the induction of angiogenesis may define a novel mechanism of relapse to Enzalutamide.

Methods: Preclinical experiments were conducted in LNCaP tumors and established human prostate cancer cell lines. Tumour growth, intra-tumoral hypoxia and blood vessel density were measured *in vivo*. AR expression, activation and target gene expression were measured *in vitro*. Effects of Enzalutamide on hypoxia-driven, disease-progressing pathways and genes of interest and the role of these genes in resistance to Enzalutamide was investigated.

Results: Enzalutamide promoted persistent hypoxia in LNCaP tumours *in vivo*, followed by increased blood vessel density and restoration of oxygen tension (>14 days). *In vitro*, hypoxia increased AR expression and transcriptional activity in LNCaP cells and sustained but did not further potentiate high basal AR and ARv7 activity in 22Rv1 cells. Enzalutamide failed to attenuate the concurrent hypoxia-induced HIF-1 and NF-κB signalling, resulting in up-regulation of disease-progressing genes and pathways. Administration of neutralizing antibodies to two hypoxia-regulated genes, IL-8 and VEGF prolonged Enzalutamide-mediated LNCaP tumour growth control over 28 days *in vivo* ($p < 0.001$) and re-sensitised enzalutamide-resistant LNCaP cells *in vitro*.

Conclusions: Enzalutamide-induced hypoxia upregulates the expression of VEGF and IL-8, whose multi-model signalling effects contribute to microenvironment-promoted resistance in prostate tumours.

Legal entity responsible for the study: David Waugh

Funding: Prostate Cancer UK

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32P Prognostic impact of KRAS mutation in cell-free DNA in patients with pancreatic cancer

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Background: Cell-free DNA (cfDNA) has been known to be released from tumor cells and evaluated potential biomarkers for therapeutic responses. However, the role of cfDNA in pancreatic cancer has not been well studied. Here we selected *KRAS* mutation which has been known common over 95% of pancreatic ductal adenocarcinoma (PDA) and evaluated applicability as a prognostic marker through the quantitative analysis of cfDNA and *KRAS* mutation in the patients with PDA.

Methods: Total of 106 PDA patients were enrolled in the study. The concentration and fraction of *KRAS* mutation were measured by *KRAS* screening multiplex droplet digital PCR kit (Biorad, USA) in plasma samples.

Results: KRAS mutation was detected in 97.4% of tissue samples and the correlation with cfDNA was 0.561 with 80.5% positivity. KRAS mutation concentration and fractional abundance showed the association with poor survival in both PFS ($P < .001$ and $P = 0.001$) and OS ($P = 0.003$ and $P = 0.006$) in the entire stage groups. Specially, the impact for survival of KRAS mutation concentration and fractional abundance was obvious in PFS in resectable group ($P = 0.016$ and $P = 0.02$). When we analyzed the receiver operating characteristic (ROC) curve to determine whether KRAS mutation in cfDNA have additive benefits with well-known tumor markers CA19-9, combined with KRAS mutation concentration or KRAS fractional abundance, the value of area under the curve (AUC) was significantly higher than the value calculated as CA19-9 alone.

Conclusions: This study represents that KRAS mutation concentration and fractional abundance in cfDNA could be prognostic marker in pancreatic cancer especially in resectable group.

Legal entity responsible for the study: Sun-Young Kong

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Disclosure: All authors have declared no conflicts of interest.

33P Isoform-specific functions in pancreatic adenocarcinoma

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Background: AKT/PKB is a protein kinase that plays a key role in cancer, which is expressed as 3 isoforms: AKT1 (PKBα), AKT2 (PKBβ) and AKT3 (PKBγ). Although these isoforms are remarkably similar, there is evidence that each isoform yields specific functions which may vary depending on the cell type. Even so, the underlying molecular pathways specifically regulated by each one of them are unknown.

Methods: To gain insight into the role of each isoform in the biology of human pancreatic adenocarcinoma cells, we have silenced each AKT isoform individually using 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.

Results: AKT1 silencing induced the upregulation of 57 proteins and downregulation of 58. AKT2 silencing up-regulated and down-regulated 78 and 101 respectively. AKT3 silencing resulted in the upregulation of 88 and downregulation of 93. The expression levels of 45 proteins were altered exclusively after AKT1 knockdown, while 74 proteins and 89 were specifically altered for AKT2 and AKT3 silencing, respectively. AKT1 silencing up-regulated RNA splicing, GPCR and mTOR pathways, and mitochondrial functions such as the respiratory chain, fatty acid metabolism or mitochondrial DNA synthesis. Pathways related to apoptosis and cell migration were inhibited. AKT2 silencing caused the activation of pathways related to apoptosis, splicing, protein folding and some mitochondrial functions. In contrast, other key metabolic pathways such as nucleic acid synthesis, pentose phosphate pathway, cell adhesion and PI3K signalling were down-modulated. Lastly, AKT3 silencing induced increased splicing and mitochondrial functions, regulation of gene expression and snRNA processing. In this case, the pentose phosphate pathway, cell adhesion, apoptosis, protein synthesis and nucleic acid synthesis were also inhibited.

Conclusions: AKT isoforms have specific functions in pancreatic adenocarcinoma. The individual silencing of each isoform induces a differential alteration of molecular pathways involved in main cellular processes.

Legal entity responsible for the study: D. Escors

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Disclosure: All authors have declared no conflicts of interest.

34P High chemopreventive and therapeutic efficacy of Id1 inhibition in KRAS-mutant (KM) adenocarcinoma (AD) non-small cell lung cancer (NSCLC)

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Background: Id1 is an independent prognostic factor in NSCLC-AD. Id1 silencing impairs cell viability and migration of NSCLC-AD cell lines. KRAS is the most frequently mutant gene in NSCLC with no specific therapies clinically available. Here we evaluate Id1 as a potential chemopreventive and therapeutic target in a humanized mouse model of KM NSCLC-AD.

Methods: Several human lung AD cell lines with known mutations (H1792-604, H2009, H358, H1568, H1437, H1703 and H2126) were selected for Id1 silencing using inducible short hairpin RNA (shRNA). Humanized AD xenograft mouse models were generated by subcutaneous injection of H1792-604 and H2009 cell lines (Id1 silenced or Id1 wild type) in flanks of immunodeficient mice. Id1 silencing was activated at the time of tumor cell inoculation (chemoprevention assay) or once the tumors were established (therapeutic assay).

Results: Id1 inhibition was achieved in all selected cell lines compared to their controls. In vivo, in the chemoprevention assay we observed a significant decrease in tumor volume in mice injected with Id1 silenced H1792-604 cells (60% ± 32.39) compared to the control group (356.29% ± 115.32) ($p < 0.001$). Moreover, mice injected with Id1 silenced H2009 cells never developed tumors compared to control mice (168.35 ± 68.71) ($p < 0.001$). In the therapeutic assay, the activation of inducible silencing of Id1 in established tumors induced a significant reduction of tumor volume in both xenograft models. Id1 inhibition induced a partial response in 40% of the tumors after injection of H1792-604 cells and in 100% of tumors in H2009 inoculated mice.

Conclusions: These findings encourage further evaluation of *Id1* as a potential therapeutic target in KM NSCLC-AD patients.

Legal entity responsible for the study: Clínica Universidad de Navarra

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Disclosure: All authors have declared no conflicts of interest.

36P Synergistic effect of vismodegib and cisplatin in NSCLC models via autophagy

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Background: Platinum-based chemotherapy still represents the standard first-line approach for NSCLC patients, although primary or secondary resistance is frequently observed. Recently the Shh pathway has been associated with resistance to platinum-based chemotherapy in NSCLC. The aim of this work is to investigate whether a combined treatment with cisplatin and the Hedgehog-pathway inhibitor vismodegib could potentiate the anti-tumour effect and to explore possible mechanisms of this synergy.

Methods: Two Human NCSLC cell lines A549 and H460 were treated with single agent Cisplatin, single agent Vismodegib and a combination of the two drugs. MTT cytotoxicity assays were performed and the data were analysed with CompuSyn software. Experiments of apoptosis and cell cycle were done by using flow cytometer. Immunofluorescence with lysoTracker as well as western blot (WB) analysis for the LC3B protein were performed to analyse autophagy.

Results: The CompuSyn analysis showed an important synergistic effect of cisplatin + Vismodegib. Combined treatment induced a significant increase in cellular apoptosis compared with single agent cisplatin. The cell cycle analyses revealed a block in S-phase with the combination treatment. The lysoTracker immunofluorescence assay showed that cisplatin induces an increase of autophagy, while the combination with vismodegib strongly reduces it, finally reverting this effect. These findings were confirmed by WB analysis for LC3B which is significantly increased by single agent cisplatin and reduced by the combined treatment.

Conclusions: Combined treatment with cisplatin and vismodegib has a synergistic effect with an increase in cancer cell apoptosis. Autophagy has been described as a mechanism through which cancer cells escape cisplatin-induced cytotoxicity. Combining cisplatin with vismodegib leads to an inhibition of autophagy, so that it could suggest a new therapeutic approach.

Legal entity responsible for the study: Università della Campania "Luigi Vanvitelli"

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Disclosure: All authors have declared no conflicts of interest.

37P Association of the rs4567312 variant in the leptin receptor gene with plasma leptin concentrations and lung cancer incidence in the PREDIMED study

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Background: Many studies have found leptin related genes involved in tumorigenesis and have suggested it may play a role in the pathogenesis of lung cancer. Leptin Receptor (LEPR) is expressed in many tissues and cells, including lung mucosal cells. LEPR was reported to be associated with tumor cell proliferation and angiogenesis. Our objective has been to estimate the association between the rs4567312-LEPR gene and lung cancer incidence in a Mediterranean population.

Methods: We analyzed 1094 participants (398 men, 696 women) recruited in the PREDIMED-Valencia Study. Participants were high cardiovascular risk subjects aged 67±6 years at baseline. PREDIMED is a multicenter randomized, controlled trial aimed at assessing the effect of the Mediterranean diet (MedDiet) on cardiovascular prevention (primary outcome). Cancer incidence was a secondary outcome in this trial. Demographic, clinical, life-style, biochemical, and genetic variables were obtained. Subjects were followed-up prospectively from 2003 to 2014 (in the extended-follow-up).

Results: We detected 12 new cases of lung cancer from 2003 to 2014 (1.1% cumulative incidence). Tobacco smoking was strongly associated with lung cancer incidence (91.7% of current or former smokers in lung cancer subjects vs 41.5% in the non-cancer participants ($p = 0.001$). In the whole population, prevalence of the rs4567312 polymorphism was: 95.5% CC, 4.4% CT and 0.1% TT. We also detected in the whole population an association between this polymorphism and plasma leptin concentrations, 26.9±22.9 ng/mL in CC vs 18.4±16.7 ng/mL in T carriers ($p = 0.013$). We found a strong association between the rs4567312-LEPR polymorphism and lung cancer risk, being higher in carriers of the T-allele. This association remained statistically significant (OR = 7.61; 95% CI: 1.74-33.37 for T-carriers vs CC) even after adjustment for gender, age, tobacco smoking, dietary intervention group (MedDiet vs control diet) and leptin levels.

Conclusions: T-carriers allele in the rs4567312-LEPR polymorphism presented a higher incidence of lung cancer in this Mediterranean population even after adjustment for tobacco smoking and dietary intervention.

Clinical trial identification: Controlled-trials.com number ISRCTN35739639

Legal entity responsible for the study: Instituto de Salud Carlos III and University of Valencia

Funding: Instituto de Salud Carlos III

Disclosure: All authors have declared no conflicts of interest.

38P Two-step microarray analysis of cell-free miRNA in plasma of lung cancer patients

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Background: Lung cancer (LC) is causing more than 1.3 million deaths worldwide annually. Early detection of LC is critical for survival but despite recent advancements in LC diagnostics most patients are still diagnosed at advanced stages of the disease. The situation is further complicated by high intratumor heterogeneity and general diversity of lung malignancies. Insights into cancer genetics have kindled interest in molecular cancer diagnostics. One of the lucrative sources of prospective LC biomarkers is cell-free circulating miRNAs. These small non-coding RNAs are frequently deregulated in LC. It is also known that miRNAs can travel in bodily fluids for extended periods of time, shielded from degradation by membrane vesicles or other biopolymers. Recently, specific subsets of miRNAs associated with tumor phenotypes and disease progression have been found circulating in blood of cancer patients and suggested as potential biomarkers for LC.

Methods: In the present study, we have investigated the profiles of circulating miRNAs in blood plasma of LC patients and healthy individuals (HD) in order to identify potential markers for lung cancer diagnostics. Small RNAs were isolated from blood plasma of 20 LC patients and 10 healthy individuals (HD) using protocol reported earlier (Zaporozhchenko et al, Anal Biochem, 2015). Profiles of miRNA expression were obtained using miRCURY LNA miRNA qPCR Panels Plasma/Serum (Exiqon). Ratio based normalization was applied to all miRNA's with call rate higher than 80%.

Results: Statistical comparison using two-way ANOVA identified 241 ratios (98 individual miRNAs) with significantly different expression between LC patients and HD ($p < 0.05$ after Benjamini-Hochberg correction). Using LASSO penalization models and manual filtering of miRNAs associated with haemolysis, 7 miRNA ratios were identified as best predictors of cancer. Extended set of miRNAs ($n = 19$) was selected for further verification in an independent sample of 30 LC patients, 20 HD and 10 patients with hyper- and metaplastic endobronchitis using custom miRCURY LNA miRNA qPCR Pick & Mix Panel.

Conclusions: Based on expression in both data sets 5 ratios containing 7 miRNAs were selected for further validation in an extended cohort of LC and cancer-free individuals.

Legal entity responsible for the study: Laboratory of Molecular Medicine, SB RAS Institute of Chemical Biology and Fundamental Medicine, Novosibirsk, Russian Federation

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Disclosure: All authors have declared no conflicts of interest.

39P DNA methylation of the CYP1A1 and GSTP1 genes and incidence of major cancers (lung, breast and colon) in the PREDIMED-Valencia study

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Background: DNA methylation is an epigenetic determinant of gene expression. Cytochrome P450 (CYP1A1) is a phase 1 xenobiotic metabolizing enzyme. Glutathione S-transferase P1 (GSTP1) detoxifies metabolites and regulates cellular chemical stress and death. Methylation changes in these genes could play a role in the incidence of cancer. Our aims were to analyze DNA-methylation of selected CpG islands in the CYP1A1 and GSTP1 genes at baseline in subjects who had incident cancer and paired controls, and to determine if DNA methylation in cancer patients changed from baseline to the time close to cancer diagnosis.

Methods: We followed-up 1094 subjects (aged: 67±6years) of the PREDIMED-Valencia study prospectively from 2003 to 2014. Cancer incidence was a secondary outcome in our trial. We analyzed 69 cases of incident cancer (lung, breast and colon) during this follow-up period, and 69 paired controls free of cancer. We analyzed DNA-methylation levels of the CYP1A1 and GSTP1 genes at baseline in both groups. Quantitative DNA methylation analysis was undertaken by MALDI-TOF mass spectrometry. We evaluated methylation levels on chromosome 15 (region: 74726090 - 74726460 base pairs from promoter) and chromosome 11 (region: 67583556-67583896 base pairs from promoter).

Results: We detected statistically significant differences in DNA methylation levels at baseline in the CYP1A1 and GSTP1 genes between cancer cases and controls (P=0.008 for the CpG site 26-27 of the CYP1A1 gene and P=0.049 for the CpG 10-11 island at the GSTP1 gene). We detected statistically significant changes in DNA methylation prospectively in cancer patients. DNA methylation at the CpG 4 (CYP1A1 gene) was 0.020±0.034 at baseline vs 0.006±0.013 close to cancer diagnosis (P=0.044). For the GSTP1 gene, methylation of the CpG 34-39 prospectively increased from 0.327±0.046 at baseline to 0.345±0.053 (P=0.014) close to cancer diagnosis.

Conclusions: We have detected differences in DNA-methylation of selected CpG Islands of the CYP1A1 and GSTP1 genes at baseline, between future diagnosed cancer subjects and cancer-free controls. Moreover, in patients subsequently diagnosed with cancer, a change in DNA methylation was observed between baseline and close to the time of cancer diagnosis. This suggests a dynamic influence of DNA methylation that could be modulated for prevention.

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40P Regulation of glucose transporters by protein kinases in cancer cells

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Background: Cancer cells require increased glucose supply to sustain proliferation. One mechanism involves increased expression of glucose transporter (GLUT) genes. But insulin has revealed that protein phosphorylation is another key mechanism in glucose uptake regulation: insulin binding to responsive cells triggers a signalling cascade with phosphorylation of TBC1D4, a negative regulator of endosomal GLUT trafficking,

so that more transporters are inserted into the plasma membrane. Previous work from the host lab has identified the family of WNK protein kinases and shown that WNK1 can also phosphorylate TBC1D4 and promote GLUT translocation to the cell surface. Our objective is to understand the contribution of WNK1 to glucose uptake in colorectal cancer cells. Our objective is to understand the contribution of WNK1 to glucose uptake in colorectal cancer cells.

Methods: To characterize the role of WNK1, various colorectal cell lines were first cultivated with different glucose concentrations. Levels of GLUT1 at the cell surface were compared under these conditions and the effect of depleting WNK1 expression by siRNA determined.

Results: For selected conditions, key cell cycle or apoptotic marker proteins were analysed by Western blot and revealed higher apoptotic and cell-cycle arrest phenotypes in WNK1-depleted cells cultured in low glucose medium. In order to dissect key phosphorylation events involved in GLUT1 regulation, mass spectrometry analysis revealed that WNK1 phosphorylates TBC1D4 and the functionally related TBC1D1 at unique Serine residues. The corresponding phospho-mimetic mutants are currently being tested for their ability to increase GLUT1 translocation.

Conclusions: Together, these studies will elucidate the molecular details regulating the translocation of glucose transporters in cancer cells and have the potential to identify novel therapeutic targets.

Legal entity responsible for the study: Peter Jordan

Funding: Fundação para a Ciência e Tecnologia BioISI - Biosystems and Integrative Sciences Institute

Disclosure: All authors have declared no conflicts of interest.

41P Signal transduction pathways regulating alternative splicing of tumor-related RAC1b

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Background: In colon cancer distinct genetic subtypes have been described, one of which involves overexpression of RAC1b, a variant generated by alternative splicing. Aberrant splicing is known to occur in cancer and can be caused by mutation in a gene or splicing factor but also represents a dynamic response to oncogene-induced cellular signaling and in this case it may be pharmacologically targeted. Here we explore how signaling pathways are involved in the deregulation of alternative RAC1b splicing in colorectal tumor cells.

Methods: HT29 colorectal cells represent serrated colorectal tumors with *BRAF* gene mutation V600E in one allele and RAC1b overexpression. Cells were transfected with shRNA vectors directed against target candidate protein kinase transcripts and their effects on RAC1b levels analyzed 24h later by Western Blot and qRT-PCR. Treatment with kinase inhibitors or anti-inflammatory drugs was performed 24h prior to cell lysis.

Results: Two kinases, SRPK1 and GSK3β, were found required to sustain RAC1b levels and both were shown to act upon the phosphorylation of splicing factor SRSF1, which binds to and promotes the inclusion of the alternative exon in RAC1b. SRPK1 knockdown or pharmacological inhibition reduced SRSF1 phosphorylation decreasing its nuclear translocation and concomitantly RAC1b splicing. The same regulatory pathway was also found to be controlled by GSK3β. Interestingly, GSK3β phosphorylation was identified to serve as target for the anti-inflammatory drug ibuprofen, which inhibits RAC1b overexpression.

Conclusions: Together, our results demonstrate that oncogenic signal transduction pathways deregulate alternative splicing and this may be drug revertable.

Legal entity responsible for the study: Peter Jordan

Funding: Fundação para a Ciência e Tecnologia

Disclosure: All authors have declared no conflicts of interest.

42P Preserving tumor heterogeneity: A microfluidic reactor for ex vivo preservation of colorectal cancer biopsies

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Background: Foreseeing treatment outcome in cancer patients is still a challenge that needs to be addressed. Tumors are complex structures, where the interaction between the tumor cells and the surrounding microenvironment regulates key processes in cancer progression, such as angiogenesis, evasion and modulation of the immune system response, and invasiveness. These interactions confer tumors a high heterogeneity not only inter-patient but also intra-patient. In vitro experimental models have been developed to preserve this heterogeneity present on tumor biopsies by the use of rotary wall and perfused bioreactors. However, the complexity and size of the bioreactors prevent from visual inspection of the sample and the realization of a high-throughput screening. The present work focuses on the combination of microfabrication techniques and microfluidics to downsize classic experimental models. The developed methodology requires only microliter size sample, and allows real time optical inspection.

Methods: A microscopy slide size optically transparent microfluidic bioreactor (μbioreactor) was designed and developed to preserve high cellularity on complex samples through constant perfusion. Colorectal carcinoma (CRC) biopsies were taken after previous patient consent was obtained. CRC biopsies were perfused by cell culture media in the μbioreactor during one week. After perfusion, CRC biopsies were histologically processed, stained and characterized by immunofluorescence.

Results: High cellularity was observed in CRC biopsies after one week of perfusion. Stromal and parenchymal preservation was confirmed by both, histological staining and immunofluorescence.

Conclusions: The use of microfluidic bioreactors can be successfully used to preserve CRC biopsies, maintaining cell heterogeneity while allowing optical inspection. The use of small sample volumes (microliters) allows high throughput screening using regular biopsy samples, a key feature to achieve personalized treatments in cancer.

Legal entity responsible for the study: University of Zaragoza

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44P Role of ICAM-1/LFA-1 interaction in the angiogenic and desmoplasic response in liver metastasis

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Background: The colorectal cancer is one of the most common cancers in the world being the main cause of death the metastatic spread to the liver. During metastatic progression, a stromal and tumor cell crosstalk mediated by hepatic ICAM-1 and tumor LFA-1 interaction modulate the tumor microenvironment through an inflammatory and immune response. Additionally, a matrix remodeling and angiogenic response is also associated with tumor progression. The main cell type associated to these processes is the fibroblast associated to the tumor. Thus, the aim of this work is to elucidate the effect of ICAM-1/LFA-1 interaction during the angiogenic and desmoplasic response during liver metastatic progression.

Methods: To do so, the effect of ICAM-1/LFA-1 interaction on the tumor progression and recruitment of cancer associated fibroblasts was analyzed by an experimental metastasis assay in vivo and a modified Boyden chamber migration assays in vitro, after either activation of tumor cells with sICAM-1 or blocking of ICAM-1/FA-1 interaction. In addition, the effects of LFA-1 tumor depletion on tumor migratory potential induced by tumor-activated fibroblasts derived factors were analyzed. Also, the effect of the modulation of this pathway on MMPs protein and angiogenic gene expression levels was measured by zymography and qPCR, respectively.

Results: In vivo and in vitro assays showed an increase on fibroblast and tumor cells recruitment after activation of tumor LFA-1 activation by binding with sICAM-1 which was abrogated after blocking of LFA-1. Moreover, the expression levels of MMPS and other proangiogenic factors were decrease after the blockage of ICAM-1/LFA-1 interaction. Also, the collagen deposition was increased after LFA-1 activation and diminished by LFA-1 blocking.

Conclusions: The interaction of ICAM-1 with tumor LFA-1 favors the recruitment of fibroblast within the tumor mediated by a modulation of pro-desmoplasic factors. This favors the remodeling of the tumor stroma and the angiogenic response and promotes tumor metastatic progression. Thus, LFA-1ICAM-1 interaction might be pointed out as a potential target for therapy of the metastatic disease.

Legal entity responsible for the study: Department of Cellular Biology and Histology, University of the Basque Country, School of Medicine and Nursery

Funding: Basque Government

Disclosure: All authors have declared no conflicts of interest.

45P Role of discoidin domain receptors in extracellular matrix remodeling during tumor-host interaction in liver metastasis

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Background: Metastasis is the main cause of death for most solid tumors. The liver is a metastasis-susceptible organ and represents the first most common site for colorectal cancer (CRC). During tumor progression, the unique hepatic microenvironment suffers a reorganization involving the interaction between the tumor, the different hepatic stromal cells and the extracellular matrix (ECM), which is under an extreme remodeling. Among the receptors involved, discoidin domain receptors (DDR-1 and -2), a class of tyrosine kinase receptors for fibrillar collagen, are emerging as new therapeutic targets in cancer treatment, including colorectal. Aim: We aim to elucidate the implication of DDRs in the prometastatic properties of the CRC cells and stromal cells in the liver.

Methods: First, the expression of DDRs on the stromal cells under tumor activated conditions and on tumor cells in the presence of tumor-activated stromal factors was assessed at protein levels. Second, this was related to the migratory potential under the same conditions. Finally, metalloproteinases expression, known to be induced by DDRs activation and involved in cell migration and ECM remodeling, was determined by western blot and zymography.

Results: DDRs expression was inversely altered in macrophages and fibroblasts after their activation by tumor derived factors. The expression of DDRs on CRC cells was decreased by factors derived from stromal cells. These DDRs deregulated expression was related to changes in the migratory capacity of tumor and stromal cells. Moreover, MMP-9 and MMP-14 expression increased in the stromal cells activated by tumor factors, while TIMP-2 expression was higher in fibroblasts but lower in macrophages. Also, the activation of CRC cells by either fibroblasts or macrophages derived factors induced a differential expression of MMP-2, MMP-9 and MMP-14.

Conclusions: The differential expression of DDRs by cells in the tumor microenvironment could redirect the expression of MMPs inducing the migratory capacity of CRC cells. In conclusion, tumor and stromal cells crosstalk may dysregulate the ECM deposition related to DDRs expression contributing to the extensive stroma remodeling in CRC metastatic diseases.

Legal entity responsible for the study: University of the Basque Country (UPV/EHU)

Funding: University of the Basque Country (UPV/EHU)

Disclosure: All authors have declared no conflicts of interest.

46P Novel role of apatinib as a multi-target RTK inhibitor in the direct suppression of hepatocellular carcinoma cells

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Background: Although apatinib has been demonstrated with potential antitumor activity to multiple solid tumors, the underlying mechanism of apatinib for the treatment of hepatocellular carcinoma (HCC) remains unclear. In the present study, we explore if there is any direct suppression effect of apatinib on HCC cells and its relevant targets.

Methods: To determine the role of apatinib, we investigated its effect on viability, colony formation, apoptosis, migration of 6 HCC cell lines in vitro, and HCC progression in mice model. Using a phospho-receptor tyrosine kinase pathway array with 49 different tyrosine kinases, we screened and verified the tyrosine kinase targets involved in apatinib therapy.

Results: Apatinib treatment significantly inhibited HCC cell viability, proliferation, colony formation, migration, and enhanced cell apoptosis in a concentration-dependent manner ($p < 0.05$). Furthermore, apatinib showed a favorable anti-tumor growth effect (71% of inhibition ratio, $p < 0.05$) in the established human HCC xenograft mice model with good safety. RTK pathway arrays and western blots analysis demonstrated apatinib significantly down-regulated the phosphorylation levels of several tyrosine kinase receptors, especially PDGFR-α and IGF-IR, and inhibited Akt phosphorylation.

Conclusions: These novel data suggested that the apatinib may have a direct anti-HCC effects as a direct multi-target RTK inhibitor of HCC cells and a promising potentiality in HCC clinical therapies.

Legal entity responsible for the study: Xiaojin Li

Funding: None

Disclosure: All authors have declared no conflicts of interest.

47P GATA6 exhibits tumor suppressive effects in hepatocellular carcinoma

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Background: GATA6 is a transcription factor that regulates endoderm differentiation and lineage specification. Dysregulation of GATA6 expression had been reported in cancers of endoderm-derived organs such as the lungs, stomach and pancreas. The aim of this study is to determine the clinical significance of GATA6 in hepatocellular carcinoma (HCC) and characterize its potential functional roles.

Methods: GATA6 mRNA expression was assessed in 74 clinical HCC samples by quantitative polymerase chain reaction (qPCR). Correlation between GATA6 expression and clinicopathological parameters was analyzed. Stable GATA6 knockdown clones were established by a lentiviral-based approach in HCC cell line Huh7, which showed relatively high endogenous GATA6 expression. Functional effects upon GATA6 manipulation were investigated by cell proliferation, migration, invasion and tumorsphere formation assays *in vitro*.

Results: GATA6 expression was significantly downregulated in HCC tumor tissues when compared with the corresponding non-tumoral liver tissues ($p = 0.007$). A lower GATA6 expression was correlated with poorer cellular differentiation ($p = 0.004$). Silencing of GATA6 stimulated HCC cell proliferation, and promoted cell invasive and migratory abilities *in vitro*. This increase in metastatic capacity was mediated through the activation of epithelial-mesenchymal transition (EMT), as demonstrated by the loss of E-cadherin and gain of vimentin protein expression levels. Suppression of GATA6 augmented the self-renewal ability of HCC cells as demonstrated by the enhanced number and size of tumorspheres formed in both primary and secondary generations. In addition, the expression of various stemness markers such as Nanog, Oct4 and Sox2 were upregulated upon GATA6 silencing.

Conclusions: Our findings suggest that GATA6 is downregulated in HCC which may help to convert HCC cells to a more poorly differentiated state and enhance proliferation, self-renewal ability and metastatic potential.

Legal entity responsible for the study: Department of Pathology, Li Ka Shing Faculty of Medicine, The University of Hong Kong

Funding: None

Disclosure: All authors have declared no conflicts of interest.

48P The effects of 5-fluorouracil (5-FU) on TGF-β-related signaling molecules

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Background: By identifying the mechanism of therapeutic effects of the combination of interferon alpha (IFNα)-2b and 5-fluorouracil (5-FU) on advanced hepatocellular carcinoma (HCC) with portal venous invasion[1], we recently found that 5-FU increased both the expression and secretion of transforming growth factor (TGF)-β in HepG2 cells. In this study, we analyzed the effects of 5-FU on TGF-β-related signaling molecules.

Methods: Hepatoma cells (HepG2 and HuH7) were treated with 5-FU, IFNα-2b, and the combination of 5-FU and IFNα-2b. The total and/or phosphorylated protein levels of TGF-β-related signaling molecules were detected by western blot analysis. Additionally, the effects of above-mentioned treatments on the epithelial–mesenchymal transition (EMT) of the cells were evaluated by performing invasion and migration assays.

Results: With respect to the TGF-β-induced apoptosis signals, 5-FU inhibited not only the phosphorylation of SMAD2, but also reduced the total protein levels of SMAD2, SMAD4, and pINK4b. Conversely, 5-FU stimulated the phosphorylation of TGF-β-induced EMT molecules, such as ERK and JNK, but not p38MAPK. Accordingly, the protein levels of E-cadherin were reduced in the cells treated with 5-FU. On the other hand, IFNα-2b did not affect the levels of TGF-β-induced EMT molecules, whereas the combination of 5-FU and IFNα-2b neutralized the effects of 5-FU on TGF-β-related signaling molecules and restored their protein levels to those observed in the control. Interestingly, the phosphorylated protein levels of SMAD2 and the total protein levels of E-cadherin and p15INK4b increased in 5-FU-stimulated HUH7 cells, but not in HepG2 cells. Furthermore, 5-FU stimulated both cell invasion and migration in HepG2 cells, whereas the combination of 5-FU and IFNα-2b abolished these effects of 5-FU.

Conclusions: Our data suggest that 5-FU induces the EMT of hepatoma cells through TGF-β, and that the higher efficacy of the combination therapy of 5-FU and IFNα-2b results from the inhibition of these effects of TGF-β. The differences observed between HepG2 and HUH7 cells in response to the stimulation with 5-FU indicate that the efficacy of the therapy may differ between patients with hepatitis B (HBV) or C virus (HCV) background.

Legal entity responsible for the study: Iwate Medical University

Funding: Japan Society for the Promotion of Science (JSPS)

Disclosure: All authors have declared no conflicts of interest.

49P Gene mutations involved in drug resistance in liver cancer cells using a new rna-seq data analysis workflow

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Background: According to Global Cancer Statistics (GCS) Hepatocellular carcinoma (HCC) is the 5th most common and 2nd deadliest cancer in the world. The incidence of HCC has increased over the past decades but still an effective therapy has not been developed. Sorafenib, which is the only FDA approved agent, can improve the patient survival just for a few months, therefore liver transplantation is the most efficient way of treatment up to date. In this study, we offer potential drug targets by analyzing the relationship between mutation status and drug treatment response of well-differentiated Huh7 and poorly-differentiated Mahlavu liver cancer cells.

Methods: PI3K/Akt pathway is hyperactive in ∼%40 of HCC. We determined the characterized and determined IC_{50} values of Sorafenib, PI3Ka and b inhibitors and their combinations. RNAseq experiment were performed with the inhibitor treated cells. The RNAseq data of each cancer cell line (as control) was compared to treated samples. Somatic mutations associated with drug resistance were comparatively identified with RNAseq data workflow wrapped in our laboratory using GATK-MuTect tool (Cibulskis, 2013). The results were further filtrated to obtain the missense mutations. The mutated genes that were identified during the chemical knockdown studies were further analyzed in patient survival data. The functional studies were performed by gene silencing.

Results: SLC39A5, FRG1, PPHLN1 and SRP9 gene mutations were found to be shared among all drug resistant cells. Mutated genes were shown to be associated with cancer perseverance and aggressiveness. In addition, we found an unknown transcript called CTC512. The functional studies demonstrated that once these genes were silenced, the cellular growth was prevented. Gene silencing showed the alteration of the cell cycle progression of drug resistant cells. The affected downstream pathways were further analyzed by western blotting.

Conclusions: Our results indicate potential target genes which are critical to be addressed due to their roles in resistance to drugs in HCC. Once the mutated genes are silenced the cancer progression is prevented. The identified genes can be considered as chemotherapeutical and disease progress targets.

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Disclosure: All authors have declared no conflicts of interest.

50P Camouflaging iRGD-EGFR anchored human cytotoxic T-lymphocyte membranes to the surface of nanoparticles combined with low-dose irradiation: New approach to enhance drug-delivery targeting in gastric cancer

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Background: We report a biomimetic delivery platform based on human cytotoxic T-lymphocyte membranes. In this platform, T-lymphocyte membranes were camouflaged to the surface of poly-lactic-co-glycolic acid nanoparticles, with local low-dose irradiation (LDI) as a chemoattractant. These carriers were further anchored with the recombinant protein anti-EGFR-iRGD, improving tumor accumulation, facilitating tumor uptake.

Methods: The T-lymphocyte membrane coating was verified by dynamic light scattering, transmission electron microscopy and confocal laser scanning microscopy. The particle phagocytosis study was performed using a human phagocytic cell line. In vivo NIR fluorescence imaging was performed to monitor the route of nanoparticles. EGFR expression of tumor cells was tested before and after LDI.

Results: This new platform reduced phagocytosis of macrophages by 23.99% ($p = 0.002$). iRGD-EGFR anchored T-lymphocyte membrane-encapsulated nanoparticles accumulated in tumor site more than unfunctionalized groups, while LDI significantly enhanced the targeting ability. LDI could up-regulate EGFR expression on tumor cells, which was important in the process of localization of iRGD-EGFR anchored T-lymphocyte membrane-encapsulated nanoparticles in tumors.

Conclusions: This new platform included both the long circulation time and tumor sites accumulation ability while LDI could significantly enhance the tumor accumulation ability.

Legal entity responsible for the study: National Natural Science Foundation of China

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Disclosure: All authors have declared no conflicts of interest.

51P Delivery of paclitaxel-loaded erythrocytes-based nanoparticles using injectable albumin hydrogel for regional chemotherapy

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Background: Peritoneal dissemination often occurs in advanced gastric cancer (GC) patient. However, systemic chemotherapy alone has limited effect on peritoneal metastases. The purpose of this work is to fabricate a regional nanomedicine delivery system with injectable hydrogel, to investigate the sustained drug release, biocompatibility, degradation, and the therapeutic efficacy on advanced GC.

Methods: The injectable hydrogel gelling at body temperature was synthesized by one-step esterification of albumin and polyethylene glycol. The paclitaxel-loaded nanoparticles (PRNP) were prepared by encapsulating the drug in erythrocytes membrane ghost and embedded into the hydrogel (PRNP-Gel). The physical and chemical performances were characterized by dynamic light scattering, electronic microscope and SDS PAGE. The drug loading content, hemocompatibility, degradation, drug release, drug accumulation at tumor site, and anti tumor efficacy was also investigated.

Results: The PRNP-Gel suspension gelated in 15 min after subcutaneous injection. The diameter of PRNP in hydrogel was 133.1 ± 1.6 nm, drug loading efficacy and content were $85.45 \pm 1.32\%$ and $22.10 \pm 0.25\%$, respectively. 37.9% of the loaded paclitaxel was released in 196 h *in vitro*, demonstrating the sustained release properties of PRNP-Gel. No hemolysis was detected within the concentration up to 10 mg/mL, and the PRNP-Gel degraded completely in 200 days after injection. The IC50 of PRNP against MKN45 gastric cancer cells, determined by MTT, was 15.16 ng/mL. *In vivo* antitumor evaluation found that, the tumor growth inhibition of MKN45 on tumor bearing mice was 64.5% of PRNP-Gel group, which was higher than the PRNP (40.0%, $P < 0.05$) and Taxol (33.8%, $P < 0.05$). The average tumor weight was 74.9 ± 40.1 mg, while they were 194.6 ± 90.9 mg and 199.6 ± 73.9 mg in PRNP and Taxol respectively ($P < 0.05$).

Conclusions: The biocompatible and degradable drug delivery system could release chemotherapeutics in a long-term and sustained manner, exhibited an enhanced drug accumulation at tumor site, resulting in the superior antitumor effect *in vitro* and *in vivo*. This work provided a new strategy of therapy for advanced GC.

Legal entity responsible for the study: Hanqing Qian

Funding: National Nature Science Foundation of China

Disclosure: All authors have declared no conflicts of interest.

52P Effect of apatinib combined with 5-fluorouracil (5-FU) on proliferation, apoptosis and invasiveness of gastric cancer cells

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Background: To investigate the effect of apatinib, a small-molecule tyrosine kinase inhibitor, combined with 5-FU on proliferation, apoptosis and invasiveness of human gastric cancer cells AGS, and provide experimental basis for the treatment of two drugs combination in gastric cancer in clinic.

Methods: The expression of vascular endothelial growth factor receptor 2 (VEGFR2) protein in human umbilical vein endothelial cells (HUVEC) and human gastric cancer cells were assessed by western blotting. 4-methyl-teerazolium (MTT) assay and flow cytometry were used to assess the cytotoxicity and apoptosis effects of the cells in response to control, single apatinib, single 5-FU, and apatinib combined 5-FU groups. Western blotting was used to evaluate the expression of p-Akt, proliferating cell nuclear antigen (PCNA), Caspase-3 and the invasiveness differences of the four groups were detected by wound healing assay and matrix metalloprotein-2 (MMP-2), E-cadherin gene amplification were measured by RT-PCR.

Results: AGS had the expression of VEGFR2. Compared with single drug groups, apatinib combined with 5-FU could significantly suppress the growth, proliferation and induce apoptosis of human gastric cancer cells in time and dose-dependent manners ($P<0.05$). Western blotting dispalyed p-Akt and PCNA expression decreased after AGS cells treated with apatinb combined 5-FU. Wound-healing assay showed the invasiveness of AGS cells was inhibited and probably through down-regulating MMP-2 and E-cadherin amplification in combined group ($P<0.05$).

Conclusions: Our study points that apatinib combined 5-FU could inhibit the proliferation of AGS gastric cancer cells by down-regulating the expression of p-Akt. The invasiveness of AGS cancer cell was inhibited by reduced expression of MMP-2 and E-cadherin genes, and provides a theory basis for 5-FU and apatinib combination in clinic with advanced gastric cancer patients who failed to second-line treatment but still had a good performance status.

Legal entity responsible for the study: Bangwei Cao

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Disclosure: All authors have declared no conflicts of interest.

53P One tumour, two clones: An in vitro model of intra-tumour heterogeneity

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Background: Eradication of advanced disease remains elusive in the majority of cancers including soft tissue sarcomas (STS) despite advances in our understanding of the molecular mechanisms that drive them. Targeted treatment development to date has largely relied upon data derived from all cells within a tumour sample and/or tumour cell lines. These approaches however, do not account for inherent heterogeneity of cancer cells within a single tumour and is considered an important factor that leads to treatment failure. Understanding intra-tumour heterogeneity is therefore a priority for cancer research and appropriate tumour models with sufficient availability would greatly facilitate the identification of newer targets and factors that lead to treatment resistance. We therefore aimed to develop *in vitro* models of STS that reflect intra-tumour heterogeneity.

Methods: We obtained tissue from patients having surgery for STS in Sheffield Teaching Hospitals and established primary tissue cultures. Short Tandem Repeat (STR) confirmed the same origin of both clones in both cases. DNA copy number profiling and gene expression microarray analysis were used for molecular characterisation of self-immortalised primary cell lines.

Results: One leiomyosarcoma (Shef-LMS 01) and one myxofibrosarcoma cell line (Shef-MFS 01) established two morphologically-distinct tumour cell types (culture variants) in separate long term cultures. Karyotyping and growth characteristics confirm that both variants in each case are tumour cells and they have remained in culture for over 100 passages. STR profiling confirms that in each case, both clones are derived from the same tumour. DNA copy number analysis with microarray-based comparative genomic hybridisation and gene expressson analysis shows many identical somatic copy number abnormalities (SCNA) between variants, but also numerous genomic and transcriptomic differences.

Conclusions: We believe that these genomic and transcriptomic differences provide clues to clonal evolution in these tumours and may explain the development of resistance to targeted treatment. These cell lines are therefore useful for the identification of novel targets and development of effective therapies for these tumours.

Legal entity responsible for the study: Abdulazeez Salawu

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Disclosure: All authors have declared no conflicts of interest.

54P Docosahexaenoic acid mediates susceptible cell death through differential regulation of p62/p-eIF2alpha/NRF2 in LMP1-expressing nasopnaryngeal carcinoma cells

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Background: Docosahexaenoic acid (DHA) induces apoptotic cell death through several mechanisms in cancer cells. We have previously demonstrated that DHA triggers apoptosis by increasing reactive oxygen species (ROS) accumulation and the ROS-mediated apoptosis caused by DHA is associated with Nrf2 signaling activation. Here we report that DHA-induced cell death is more susceptible through p62/p-eIF2alpha/NRF2 regulation in LMP-1-expressing nasopharygeal carcinoma (NPC) cells.

Methods: Viability of CNE-LMP1 and HONE-EBV cells was compared with CNE and HONE after DHA treatment by MTT assay. DHA-induced apoptosis was analyzed using the TUNEL assay and Western blot of cleaved form of PARP. Tissue expression of LMP-1 and p62 were observed by immunohistochemistry.

Results: Treatment of four human NPC cells (CNE, CNE-LMP1, HONE, HONE-EBV) with DHA for 24 hr resulted in a dose-dependent inhibition of cell growth. The DHA effect was due to the induction of apoptosis, given that DHA increased the cleaved form of PARP as well as the number of TUNEL-positive cells. The inhibition of CNE-LMP1 and HONE-EBV cells after DHA treatment is more susceptible. compared with CNE and HONE cells without LMP1 by MTT assay. The level of p62 and NRF2 of LMP1-NPC cells were increased after DHA pretreatment cpmpared to control NPC cells. On the other hand, the level of p-eIF2alpha produced reverse result. The activation of Nrf2 signal seems to result from decreased Nrf2 inhibitor, Kelch-like ECH-associated protein 1 (Keap1), because DHA remarkably attenuated Keap1 expression levels. Moreover, silencing Nrf2 by small interfering RNAs inhibited the cytotoxic effect of DHA, indicating that Nrf2 activation plays a positive role in the process of DHA-induced apoptosis. Increased staining for LMP1 and p62 was observed in NPC tissues when compared with the nonneplastic (chronic inflammation) tissues.

Conclusions: These results suggest that differential regulation of p62/p-eIF2alpha/NRF2 contributes to susceptible cell death by DHA in LMP-1-expressing NPC cells. Thus, utilization of DHA may represent a promising therapeutic approach for chemoprevention and treatment of human NPC.

Legal entity responsible for the study: Chungnam National University

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55P Inhibition of the ubiquitin-conjugating enzyme E2B restores the BCNU sensitivity of cancer cells by regulating MGMT ubiquitination

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Background: O^6-Methylguanine-DNA methyltransferase (MGMT) is a DNA repair enzyme that removes the mutagenic O^6-alkyl groups from guanines. 1, 3-Bis (2-chloroethyl)-1-nitrosourea (BCNU), a DNA damage reagent, is known to induce cell death of tumors and the ubiquitin dependent proteolysis of MGMT. The present study aims to enhance BCNU cytotoxicity toward cancer cells by modulating MGMT dynamics.

Methods: Human nasopharygeal carcinoma cells, including HONE-1 and TW01, and human colon carcinoma HT-29 cells were used for the BCNU treatments, siRNA knockdown, immunoprecipitation and western blot experiments. The BCNU cytotoxicity was determined using methylene blue assay. Proteins involved in MGMT ubiquitination were confirmed with immunofloresence staining and *in vitro* protein ubiquitination assays.

Results: We previously identified ubiquitin-conjugating enzyme E2B (UBE2B), a DNA repair enzyme with ubiquitin-conjugating abilities, as a critical regulator of the cell cycle in oral cancer cells. A novel role of UBE2B was further revealed in regulating MGMT dynamics in nasopharygeal carcinoma cells and colon carcinoma cells. Increased colocalization of UBE2B with MGMT was found in BCNU treated cancer cells. Depletion of MGMT or UBE2B in cancer cells resulted in decreased IC50 for BCNU. Lower MGMT expression levels were observed in UBE2B deficient cells. Overexpression of MGMT rescued the UBE2B-depleted cells from the cytotoxic concentrations of BCNU, suggesting that MGMT is a downstream target of UBE2B. The E3 ubiquitin ligase RAD18, that is known as a partner of UBE2B in facilitating PCNA ubiquitination, was analyzed to investigate the mechanism of the UBE2B regulation on MGMT. Interaction of RAD18 and MGMT was observed in cancer cells, and was enhanced under the BCNU treatments. Our results also showed that UBE2B and RAD18 contribute to MGMT ubiquitination under *in vitro* conditions.

Conclusions: Our study indicated that the UBE2B-RAD18 regulation on MGMT plays an important role in BCNU-induced cancer cell death. Thus, UBE2B inhibition may be considered as a potential strategy for cancer treatment. (This work was supported by Taiwan Ministry of Science and Technology under the grants no. NSC 103-2320-B006-036-MY3).

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56P Oral squamous cell carcinoma cells were sensitized to cetuximab by Eribulin via induction of the mesenchymal-to-epithelial transition

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Background: Inhibition of EGFR signalling has emerged as a new treatment strategy for oral squamous cell carcinoma (OSCC). Previously, we found that loss of EGFR expression in OSCC was associated with EMT, and might have functional implications with regard to resistance to cetuximab, a monoclonal anti-EGFR antibody. Eribulin (a microtubule inhibitor) reportedly renders breast cancer less aggressive, and less likely to metastasise, by triggering the mesenchymal-to-epithelial (MET) transition. Here, we

evaluated whether eribulin-induced MET was associated with re-sensitization of resistant OSCC cell lines to cetuximab.

Methods: In vitro antiproliferative activities were determined in three human OSCC lines (OSC-20, OSC-19 and HOC313) treated with eribulin. These three human OSCC represented different EMT/MET states.

Results: Interestingly, HOC313 cells (mesenchymal phenotype) were highly sensitive to eribulin in comparison with other cell lines, and significantly enhanced the antiproliferative effect of cetuximab in response to the drug. Eribulin also underwent a MET-associated gene switch that resulted in high EGFR expression in HOC313 cells, and abrogated a TGF-β-induced EMT gene expression signature.

Conclusions: Eribulin-dependent sensitization of OSCC to cetuximab is likely due to induction of MET. Combination therapies based on eribulin and cetuximab have potential as a novel treatment regimen in OSCC.

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57P In vivo study of the vaccine adjuvants prothymosin alpha and prothymosin alpha(100-109) in melanoma

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Background: The TLR agonist prothymosin α (proTα) pleiotropically stimulates immune cells via generating the appropriate cytokine milieu for their activation. The C-terminal decapeptide proTα(100-109) is considered the immunologically active moiety of proTα, as it restores in vitro the deficient immune responses of cancer patients equally well to proTα. ProTα and proTα(100-109) ligate TLR-4, signal through the TRIF/MyD88-dependent pathways, and promote the maturation of dendritic cells. The latter further stimulate T_H1-type immune responses and prime tumor antigen-reactive T cell functions. We evaluated whether proTα and proTα(100-109) function correspondingly in vivo.

Methods: C57BL/6 mice were subcutaneously inoculated with the syngeneic melanoma B16.F1 cells. Upon palpable tumor formation, mice were intraperitonealy treated with 2 cycles of GM-CSF, proTα(100-109) or proTα, in conjunction with a B16.F1-specific peptide vaccine. Tumor growth and animal survival were monitored. Splenocytes from selected animals were tested for ex vivo cytotoxicity by ^{51}Cr-release assay and CD107 expression. Excised tumors were analyzed by immunohistochemistry, while serum cytokines were quantified by flow cytometry.

Results: Both peptides therapeutically administered in melanoma-bearing mice in the presence of cancer antigens, retarded tumor growth and prolonged the survival of treated animals by 25 days. Ex vivo analysis of spleen cell cytotoxicity confirmed the in vivo induction of B16.F1-specific and non-specific anti-tumor responses. Tumors of mice treated with proTα/proTα(100-109) did not show infiltration of smooth muscle fibers and vessels, produced less melanin, presented limited necrotic areas and were characterized by sparse T cell infiltration. Sera from the same animals contained more IFN-γ, whereas the concentration of IL-4 was marginally increased.

Conclusions: Our results show that proTα and proTα(100-109) induce T_H1-biased immune responses in vivo. As both peptides are non-toxic to normal cells, their ability to orchestrate and modulate the desired anti-tumor immune responses in mice, suggests their eventual exploitation as adjuvants in anti-cancer peptide vaccines in humans.

Legal entity responsible for the study: O. Tsitsilonis

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Disclosure: All authors have declared no conflicts of interest.

58P Melanoma affects clock gene machinery of several organs in tumor-bearing mice

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Background: The accumulation of soluble factors in the tumor microenvironment and their release into the bloodstream lead to systemic effects, resulting in cancer-associated syndromes such as cachexia. Another association observed in the latter scenario is chrono-disruption, which has been related with tumor onset and development. In fact, a positive relationship between master clock integrity and healthiness has already been disclosed; however, it is unclear whether the effects of chronodisruption in cancer are locally or systemically exerted. It is known that lung adenocarcinoma reprograms liver metabolism via a pro-inflammatory response without affecting liver clock genes. Our study evaluated whether a non-metastatic skin tumor can affect clock gene machinery of other organs.

Methods: Eight to sixteen-week old C57BL/6J male mice were inoculated subcutaneously with B16-F10 cells (or PBS, control animals), single housed at 22 ± 2 °C, kept under 12/12h light/dark cycle, and received food and water ad libitum. Two weeks after inoculation mice were euthanized 2 hours after lights on (ZT2) or 2 hours after lights off (ZT14). Skin of control animals and samples of non-tumoral adjacent skin, tumor, liver, lung, and brown adipose tissue (BAT) were collected to evaluate the expression of clock genes (*Per1*, *Per2*, *Bmal1*, and *Nr1d1*) by qPCR.

Results: No oscillatory profile of clock genes was detected in skin of control animals, tumor adjacent skin, and tumor itself of inoculated animals; *Bmal1* expression was reduced in adjacent skin and tumor as compared to skin of control animals. In liver and lung tissue, *Per1* and *Per2* oscillated in control animals, and tumor inoculation did not affect this oscillatory profile. Temporal oscillation of *Bmal1* and *Nr1d1* in the liver was lost in tumor-bearing mice. In BAT, *Per1* and *Bmal1* oscillatory expression was also lost in tumor-bearing mice. In all organs analyzed. *Bmal1* transcript was reduced in tumor-bearing mice when compared to control animals.

Conclusions: The presence of a non-metastatic tumor in the skin alters clock machinery in adjacent skin, liver, lungs, and BAT. These data bring new knowledge of how tumor macro-environment affects clock machinery, resulting in a likely chrono-disruption of the organism as a result of a localized tumor in the skin.

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59P Is there receptor tyrosine kinases expression on lymphocytes in patients with renal cell carcinoma? First-in-human study

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Background: To date little is known about receptor tyrosine kinases (RTK) expression on peripheral blood mononuclear cells (PBMC) and tumor infiltrating lymphocytes (TIL) in cancer patients. The aim of this study was to evaluate expression levels of major RTK: VEGFR1, VEGFR2, PDGFRα, PDGFRβ, FGFR2 in CD45+ population of PBMC and TIL isolated from patients with clear cell renal cell carcinoma (RCC).

Methods: Tumor and blood samples were obtained from 20 patients with RCC immediately after surgical resection of primary tumor. Tumors were harvested into sterile antibiotic-containing RPMI 1640 medium (Gibco). TIL isolation was performed under modified protocol [Baldan et al., 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, VEGFR2, PDGFRa, PDGFRb, FGFR2 (all Sony Biotech) and were analyzed on NovoCyte 2000R flow cytometer (ACEA Biosciences). Expression of RTK was evaluated with NovoExpress Software.

Results: Among PBMC 72.1±21.3% cells were CD45-positive. Isolated TIL contain 19.2±5.6% CD45-positive cells. PBMC and TIL express RTK. Expression levels of RTK are summarized in the table.

Table: 59P

Expression of RTK	PBMC	TIL	*P*
VEGFR1	25.6±11.4%	31.0±27.2%	0,699
VEGFR2	23.8±11.1%	53.2±29.3%	0,096
PDGFRa	48.0±18.9%	45.4±16.7%	0,833
PDGFRb	63.3±28.7%	66.7±26.1%	0,843
FGFR2	41.2±27.8%	23.6±12.3%	0,168

Conclusions: To our knowledge, this is first study that showed significant RTK expression on peripheral and RCC-infiltrating lymphocytes in RCC patients. PBMC and TIL have similar RTK expression levels.

Legal entity responsible for the study: Ethical committee, KCRB

Funding: Kidney Cancer Research Bureau

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60P Understanding and targeting Met signalling in bladder cancer

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Background: Bladder cancer affects 430,000 patients and leads to 165,000 deaths annually worldwide. With no major advances in the management of this disease in the last 2 decades, there is an urgent need to identify therapeutic targets with validated biomarkers. Overexpression of Met, a Receptor Tyrosine Kinase, was shown to correlate with poor prognosis in bladder cancer making it an attractive target. Cabozantinib, a Met inhibitor, showed clinical activity in patients with refractory bladder cancer in a clinical trial. However, little is known about how Met exactly signals in bladder cancer and there are no validated biomarkers. This study aims at unravelling Met signalling in bladder cancer.

Methods: Western blots and confocal/low light microscopy were used to assess Met signalling and its role in wound healing in Transitional Cell Carcinoma (TCC) cells. Met expression was assessed by immunohistochemistry in tissue samples ($n = 64$).

Results: Met is overexpressed in TCC cells and in 78% of invasive bladder cancer tissues. This was associated with a shorter median survival as compared to Low Met levels (12.97 Vs 18.05 months). Stimulation of TCC cells with Met ligand, Hepatocyte Growth Factor (HGF), triggered Met activation and downstream signalling as well as wound healing, all of which were reduced with Met pharmacological inhibitors including Cabozantinib. The PI3K downstream effector AKT was highly activated upon Met activation. Moreover, class I PI3K inhibition with GDC094 significantly inhibited HGF-dependent wound healing. Interestingly, HGF triggered rapid Met endocytosis in TCC cells. Furthermore, pharmacological inhibition of endocytosis reduced Met downstream signalling.

Conclusions: We report that Met is a major target in invasive bladder cancer. Our results further suggest that PI3K may be considered as a co-target of Met to improve patients' outcome. It may also be developed as a biomarker to help select patients who may respond to Met targeted therapy. Finally, we report for the first time that, upon HGF stimulation, Met gets rapidly endocytosed in TCC cells. Furthermore, inhibiting endocytosis reduced Met dependent signalling. All together, our results open the way for novel strategies to target invasive bladder cancer.

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L. Menard: Employee: AstraZeneca.

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61P Integrated molecular signatures of TERT promoter deregulation predict disease outcomes in non-muscle invasive bladder cancer

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Background: Recent studies showed increased interest in telomere biology bladder cancer. These studies were mainly focused on hotspot TERT promoter mutations and their contribution for telomerase activation and clinical outcomes. However, the study of TERT promoter methylation, as an additional deregulatory mechanism of TERT expression, was not studied in this disease. We previously uncovered a region in the TERT promoter region (THOR – TERT hypermethylated oncological region) which is specifically hypermethylated and associated with telomerase activation in cancer tissue. In this study we aim to establish the value of this duet (TERT promoter mutations and THORMeth) in bladder cancer recurrence and progression.

Methods: To explore the impact of TERTpMut and THORMeth on TERT expression and clinical outcomes in UBC we studied two cohorts of UBC patients, 331 FFPE samples. THORMeth status was assessed using quantitative bisulfite pyrosequencing. Sanger Sequencing and ddPCR accessed TERTpMut status. TERT expression was evaluated by ddPCR. Cox proportional hazards models were used to correlate THORMeth and TERTpMut with disease recurrence and progression.

Results: THOR is a diagnostic marker for urothelial bladder cancer. THOR hypermethylated ($n = 127$, 53.6%) is associated with higher levels TERT expression ($p < 0.0001$) and is a risk factor for disease recurrence in NMIBC (Log rank $p = 0.034$) and is crucial for disease progression. TERT promoter mutations are present in all stages and grades ($n = 182$, 76.8%) and are a risk factor for disease recurrence amongst NMIBC (HR: 3.8, $p < 0.0001$). Genetic and epigenetic combined signatures in the TERT promoter allow for a clinical bladder cancer classification system based on underlying telomere biology.

Conclusions: THOR is a novel biomarker for UBC, and, as TERTpMut is able to predict disease recurrence in NMIBC. TERTpMut/highTHORMeth, comprises a distinct signature that is associated with disease progression and higher TERT expression. This fact suggests a hypothetical synergism between both mechanisms and highlights the merit of evaluating TERT promoter methylation as other deregulatory mechanism in TERT expression with implications in patients' outcomes.

Legal entity responsible for the study

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62P Dose- and regimen-dependent effects of dexamethasone on extracellular matrix of brain tissue

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Background: Dexamethasone (DXM) is commonly used in the management of glioma patients to treat intracranial edema but patients often suffer from its side effects. The molecular mechanisms of these side effects are poorly studied. DXM seems to affect extracellular matrix (ECM) especially proteoglycans (PGs) known to be a major component of the ECM in brain tissue. The aim of our study was to investigate if the effects of DXM on brain tissue PGs depend on the treatment regimen or DXM dose.

Methods: Effects of different doses and regimens of DXM treatment on the brain ECM were studied using RT-PCR and IHC in the *ex vivo* model of organotypic brain tissue culture and *in vivo* experimental animal model. The *ex vivo* organotypic culture model was chosen instead of *in vitro* cell culture model as it represents the real 3D structure of the tissue and can be used to study ECM.

Results: The most expressed PGs in rat brain tissue were syndecan-1, glypican-1, decorin, biglycan and lumican. DXM treatment of organotypic hippocampus culture ex vivo led to dose-dependent suppression of brevican, perlecan and biglycan expression and increase in expression of glypican-1, NG2 and versican. In the in vivo experiments, PGs demonstrated age-specific and brain zone-specific expression patterns in normal brain of Wistar rats. The effects of DXM on cortex and hippocampus of the experimental animals were dose- and regimen-dependent. Low-dose DXM treatment led to significant decrease in expression of most PGs in cortex but 3-fold increase in syndecan-1, perlecan and brevican expression in hippocampus. Treatment with high-dose DXM resulted in 2-6-fold increase in most of PGs expression in both brain zones. Long-term treatment led to the most dramatic changes in PGs expression on both mRNA and protein levels, completely changing their expression pattern.

Conclusions: Taken together, obtained data demonstrate an importance of DXM doses/regimens during antiglioma therapy. Long-term treatment and high doses of DXM lead to the most dramatic alteration of PGs composition in brain ECM creating a favorable niche for tumor growth and relapses.

Legal entity responsible for the study: Institute of Molecular Biology and Biophysics

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Disclosure: All authors have declared no conflicts of interest.

63P Clinical dysregulation of DNA repair by the polynucleotide kinase/phosphatase-XRCC4-DNA ligase IV in neurological disease

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Background: If not repaired, DNA double-strand breaks (DSBs) can lead to genomic instability and cell death or neoplastic transformation. The major DSB repair (DSBR) mechanism in higher eukaryotes is non-homologous end-joining (NHEJ). In NHEJ, polynucleotide kinase/phosphatase (PNKP) is the primary enzyme for processing abnormal 5'-OH and 3'-phosphate ends that prevent the final repair step by XRCC4/DNA Ligase IV (Lig IV). This processing step is thought to be mediated by an interaction between the PNKP-FHA domain and CK2-phosphorylated XRCC4 C-terminal tails.

Methods: See below.

Results: Our binding assays show tight binding between XRCC4/Lig IV and PNKP both with and without CK2-phosphorylation of XRCC4. Low-resolution ensemble structures of purified phosphorylated-XRCC4/Lig IV/PNKP ternary complex by small-angle X-ray scattering (SAXS) experiments also suggest a second phosphorylation-independent interaction between the PNKP and XRCC4/Lig IV. Hydrogen-deuterium exchange (HDX) experiments have identified a candidate for this secondary interaction site within a loop in the PNKP phosphatase domain. This site contains the clinically significant PNKP E326K mutation found in the severe form of the hereditary neurological disease MCSZ (microcephaly with early-onset intractable seizures and developmental delay). Activity assays show that the E326K mutation decreases both substrate binding and turnover in PNKP when bound to phosphorylated-XRCC4/Lig IV. Furthermore, UV laser microirradiation in cells show that the E326K mutation also disrupts recruitment of PNKP to DNA lesions.

Conclusions: We have identified a putative secondary interaction site that functionally contributes both to recruitment and catalysis of PNKP in NHEJ. Disruptions to PNKP in this region may result in decreased DNA double-strand break repair in cells and describe a molecular basis of MCSZ. Further, PNKP has other known clinical neurological significance and its presence on chromosome arm 19q has interesting implications in oligodendrogliomas. This interaction surface may prove an interesting target for small-molecule inhibition of DNA strand break repair toward novel radio- and chemo-sensitizing therapies in cancer treatment.

Legal entity responsible for the study: University of Alberta

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Disclosure: All authors have declared no conflicts of interest.

64P Effects of rottlerin and genistein through EF2K on proliferation, invasion and cell cycle/death in neuroblastoma cells

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Background: Neuroblastoma (NB) is the most common extracranial solid cancer in childhood and the most common cancer in infancy in the world. Rottlerin, a naturally occurring polyphenolic compound derived from Mallotus philipinensis, appears to have great potential in cancer therapy because of its effects on proliferation and apoptosis. Genistein is a phytoestrogen and it has been found to inhibit uncontrolled cell growth in several cancers. Recently, we learned that eukaryotic elongation factor-2 kinase (EF2K) is dramatically upregulated in many cancer cells and promotes cell survival and proliferation. Rottlerin and genistein have also showed inhibitory effects on this kinase in other solid tumours like pancreatic cancer. With this is mind, we investigated the effects of rottlerin and genistein in neuroblastoma cells.

Methods: In this study, two human neuroblastoma cancer cell lines (SH-SY5Y and Kelly) were treated with rottlerin and genistein in vitro. Cell proliferation, colony formation and invasion were assessed, and wound-healing tests, western blots (wb), cell cycle and apoptosis analysis by flow cytometry were performed.

Results: Our results showed that rottlerin and genistein treatments caused a significant reduction in cell proliferation, colony formation, and invasion/wound-healing capacity in neuroblastoma cells at concentrations of 5 μM and 30 μM, respectively ($p < 0{,}0001$). The combination of these doses also increased the level of inhibition in these analyses ($p < 0{,}0001$). Additionally, these drugs also increased the level of apoptosis and caused G1 cell cycle arrest in neuroblastoma cell lines ($p < 0{,}0001$). We showed that these treatments markedly inhibit EF2K overexpression. Our wb data suggested that EF2K may enhance tumorigenesis/metastasis through the upregulation of pro-tumorigenic/metastatic pathways in these cells and these agents may produce their anti-proliferative, anti-metastatic and apoptotic effects through EF2K downregulation.

Conclusions: In conclusion, these results indicate that rottlerin and genistein have important effects on neroblastoma cell behaviour and these effects may be caused by downregulation of EF2K.

Legal entity responsible for the study: Mumin Alper Erdogan

Funding: None

Disclosure: All authors have declared no conflicts of interest.

65P Influence of emotiogenic brain structures on tumor growth in the experiment

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Background: Stress is the pathogenetic basis of many diseases. It leads to decreasing resistance of the organism, including antitumor one. Emotional stress of a cancer patient affects the quality of life and treatment outcomes by decreasing the antitumor resistance. Therefore, correction of emotional state is an urgent task. The purpose of the study was to reveal the influence of stimulation of emotiogenic brain structures on the antitumor resistance of animals with cancer.

Methods: Transplantable solid sarcoma S45 in white outbred male rats weighing 230-250 g was used as a model of tumor growth. Implantation of bipolar stimulating electrodes in the subcortical structures of the brain was performed aseptically by stereotactic coordinates. Electrodes were implanted to nucleus lateralis septi (LS) – "positive emotiogenic structure" and to Globus pallium (GP) – "negative emotiogenic structure"; the data were compared to the values in animals without electrodes (controls). The stimulation was performed daily for 2 months without changing the stimulation current.

Results: Stimulation of emotiogenic brain structures influenced the dynamics of S45 growth, and LS stimulation caused the greatest inhibition of tumor growth.

Table: 65P

Structure	LS	GP	Controls
n	9	10	10
Initial tumor V (cm^3)	3.0±0.5	3.1±1.9	2.2±1.2
Final tumor V (cm^3)	4.7±1.1	7.5±2.2	6.8±1.6
Tumor increase (%)	53.3±2.8	186±6.5	211±6.8
Effectiveness index	1.4	0.9	
Inhibition of tumor growth (%)	30.8	10.2	

Morphological study of the thymus, spleen and lymph nodes of animals with LS showed signs of high functional activity of the organs providing a high level of resistance.

Conclusions: Electrostimulation of LS influences antitumor resistance, significantly improving it. This suggests the expediency of combining specific anticancer drugs and nonspecific effects of psychotropic drugs - anxiolytics in complex treatment of cancer.

Legal entity responsible for the study: Rostov Research Institute of Oncology

Funding: None

Disclosure: All authors have declared no conflicts of interest.

66P Systematic evaluation of the immune microenvironment of neuroendocrine tumours (NET)

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Background: Immunotherapy is currently being explored in many tumour types with encouraging results, but has not yet been evaluated in neuroendocrine tumours (NET). Our aim is to characterise the immune landscape of NET and determine which immune-modulatory pathways control the tumour infiltrating lymphocytes (TILs) in order to develop a rational approach for immunotherapy in this tumour type.

Methods: Peripheral blood and fresh tissue was obtained from consenting patients with NET, and subjected to multicolour flow-cytometry to determine the abundance of CD8+, CD4+FoxP3- effector (CD4eff) and CD4+FoxP3+ regulatory (Treg) T cell subsets and the expression of co-inhibitory and co-stimulatory checkpoint molecules on these subsets. Additionally, matched FFPE tissue was obtained for multiparametric immunohistochemistry to investigate the distribution of the immune infiltrate.

Results: Tissue from 23 NET patients including 19 mid-gut tumours (13: G1 and 6: G2) was analysed. Overall the tumours contained a higher proportion of Tregs compared with peripheral blood (8.5% vs 5%, P = 0.02) and had a CD8:Treg ratio of 18.1:24.3 respectively (P = 0.036). The co-inhibitory molecules CTLA-4 and TIM-3 showed highest expression on Tregs, while PD-1 and LAG-3 expression was similar across all T cell subsets. Co-stimulatory molecules, including ICOS, 41BB and OX-40, were also highest on Tregs, as was the recently identified co-stimulatory receptor TIGIT. Immunohistochemistry revealed that the majority of cases have <1% intratumoural CD4+ and CD8+ T cells but a higher number of peritumoural T cells from all subsets. Where present, T cells were predominantly CD8+ and intratumoural CD163+ macrophages were also identified.

Conclusions: These preliminary results provide novel insight into the immune landscape of NET, and may inform the development of targeted combination immunotherapies. Initial results suggest that checkpoint molecules, such as PD1 and LAG-3, may be potential targets in this tumour type and work is ongoing to further elucidate the immunogenic potential of NET.

Legal entity responsible for the study: University College London

Funding: None

Disclosure: All authors have declared no conflicts of interest.

67P Developing a prediction model for response to lenalidomide treatment in refractory/relapsed multiple myeloma patients

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Background: Despite improvements in treatment for Multiple myeloma (MM) achieved by novel drugs such as proteasome inhibitors (PIs) and immunomodulatory drugs (IMiDs), most patients will ultimately relapse or become refractory to their current treatment. Therefore, it is important to understand the mechanisms of therapeutic resistance in relapsed/refractory MM (RRMM) for improving treatment outcome. Recently, it was reported that serum or plasma of MM patients showed sufficiently stable miRNA signatures with prognostic impacts in MM cohorts, which can be used as minimally invasive markers for predicting and monitoring treatment outcomes. However, the expression patterns and biological implications of miRNAs are still unclear in RRMM patients receiving lenalidomide with dexamethasone (Len-dex).

Methods: We investigated the expression of serum miRNAs by genomewide miRNA array analysis and explored their predictive values in RRMM patients receiving Len-dex.

Results: We explored the associations of miRNAs with treatment outcome of Len-dex treatment and prognosis in 55 RRMMs (25 good responders and 30 poor responders) and built a prediction model for treatment response. Three miRNAs (miR-29c-3p, miR-30c-5p, and miR-331-3p) were found to be significantly down-regulated in poor responders. In survival analysis, lower expression of the three miRNAs was significantly associated with shorter time to progression (TTP) or poorer overall survival (OS). Eight clinical factors were also associated with TTP or OS. By combining the miRNA markers and clinical markers, we designed a a prediction model for response to lenalidomide treatment in RRMM patients. Our model showed better prediction power (AUC=0.855, sensitivity 84%, specificity 76%, and accuracy 81%) than international staging system (ISS) based prediction.

Conclusions: Our results suggest the potential of circulating miRNAs as minimally invasive markers for treatment response and prognosis in RRMM patients.

Legal entity responsible for the study: This study was approved by the Institutional Review Board of The Catholic University of Korea and conducted in accordance with the Declaration of Helsinki.

Funding: None

Disclosure: All authors have declared no conflicts of interest.

68P Combinatorial inhibition of mTOR and exportin-1 (XPO1) represses cell survival via metabolic modulation of pro-survival pathways in mantle cell lymphomas

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Background: MCL is an aggressive B-cell lymphoma with aberrant expression of several oncogenic effectors and requiring novel anticancer strategies. The nuclear transporter exportin-1 (XPO1) is highly expressed in MCL and is critical for cancer survival and proliferation. mTOR signaling is frequently activated and an important therapeutic target in MCL. In this study, we investigated the antitumor effects and molecular/metabolic changes induced by combined with dual mTOR inhibitor AZD-2014 and XPO1 inhibitor KPT-185 on MCL cells under the hypothesis that mTOR inhibition by AZD-2014 represses KPT-185 inducedupregulation of glycolysis.

Methods: Four MCL cell lines (Jeko-1, X138, JVM-2, and MINO), primary MCL cells, and normal bone marrow samples were utilized. Cell viability was evaluated by MTT assay. Cell cycle and apoptosis were determined by flow cytometric analysis. cDNA array, iTRAQ proteomic, immunoblotting and metabolome analysis using CE-TOF-MS were also performed.

Results: AZD-2014 enhanced KPT-185-induced the inhibition of cell growth and repression of cell viability in MCL cells but not in normal bone marrow cells. Different mTOR inhibitors (AZD-8055 and MLN0128) demonstrated similar effects. AZD-2014+KPT-185 decreased expression of the oncogenic mediator c-Myc andthe translational/transcriptional network regulator HSF1as detected by immunoblotting. iTRAQ proteomic analysis demonstrated thatthe combination caused repression of ribosomal biogenesis. Treatment with either AZD-2014 or KPT-185 depressed phospho-S6.CET-OF-MS metabolite assay showed that AZD-2014+KPT-185inhibited theKrebs cycle, and that AZD-2014 effectively repressed KPT-185-induced upregulation of glycolysis. cDNA array detected downregulation of NOD2which is known to trigger activation of MAP kinases and of NF-kappa-B signaling. Moreover, AZD-2014+KPT-185 activated AMPK, an energy stress marker in a cell type-dependent manner.

Conclusions: Our findings indicated that the combinatorial inhibition of mTOR and XPO1 identifies a novel synthetic lethality mechanism that could be exploited clinically, following satisfactory completion of pre-clinical in vivo studies.

Legal entity responsible for the study: Yoko Tabe

Funding: None

Disclosure: All authors have declared no conflicts of interest.

69P CD200 and indoleamine 2,3-dioxygenase-1 (IDO-1) overexpresion in relapsed acute myeloid leukemia patients

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Background: Immunosuppression is one of the major causes of AML pathogenesis and progression. CD200 and IDO are immunoregulatory factors which overexpressed in some solid tumors and hematological malignancies. Distinct researches have shown CD200 and IDO expression is associated with AML progression. In the current study, we simultaneously examined the expression of these molecules, as the two important factors including in immunosuppression, in the newly diagnosed and relapse AML patients to investigate their correlation with each other.

Methods: 48 PBMC samples of newly diagnosed and relapse AML patients were tested and also 32 normal subjects were employed as control. CD200 expression level was examined on cells by Flow cytometry and quantitative real time RT-PCR was used to determine the IDO-1 gene expression. Finally, data were analyzed statistically.

Results: Data showed that CD200 and IDO-1 overexpressed especially in relapsed patients. Comparison between FAB AML subgroups demonstrated no statistical differences in the case of CD200 level but expression of IDO-1 was slightly increased only in M4 subgroup in comparison to M3. Correlation analyses showed strong association between expression of CD200 and IDO-1 in all patients particularly in relapsed AML, whereas no significant correlation was found in normal subjects.

Conclusions: According to the role and overexpression of CD200 and IDO-1 in AML patients and also their two-way correlation with T-regs in disease induction and progression, simultaneous assessment of these parameters are so valuable for more exact prognosis detection. Also inhibition of all these immunoregulatory pathways could be so useful for immunotherapy outcome, especially in relapsed AML.

Legal entity responsible for the study: Tehran University of Medical Sciences

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Disclosure: All authors have declared no conflicts of interest.

70P Correlation between types of acute lymphoblastic leukemia with socio demographic factors

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Background: Acute lymphocytic leukemia (ALL) is the most predominant hematopoietic clonal disorder in children than adult. ALL classifies into two subtypes: B –ALLand T-ALL. The incidence of ALL subtype in urban areas is generally higher than rural areas. In the Western World, the predominant immunophenotype observed in ALL is B-ALL with 60-80% of total case, and T-ALL is only 15-20%. But in case of developing country like India the reverse is true. The objective of the present study is to examine and correlate T-ALL and B-ALL in leukemia patients with respect to socio-demographic factors.

Methods: During May 2015 - April 2017, total 427 ALL patients (male:female::1.9:1), age between 2-60 years attended OPD and IPD of Netaji Subhas Chandra Bose Cancer Research Institute, Kolkata, India. We have collected peripheral blood and/or bone marrow samples for immunophenotyping by FACS after taking written consent from the patients. Each sample is evaluated with a panel of monoclonal antibodies and compared the immunophenotyping data with socio-demographic factors (age, sex, economic and social status etc).

Results: The overall survival of ALL patients (with mean age 13.6 years) in 2 year is 73.6%. In our hospital, the economically weak patients (77.05%) are more abundant than economically sound patients (22.95%). Out of 427 patients, T-ALL (51.28%) is predominantly higher than B-ALL (48.71%). We found that immunophenotyping data is correlated with all the socio demographic data i.e., sex, economic and social status etc. Though disease free survival and event free survival is markedly higher in B-ALL compared to T-ALL, but we found the survival of T-ALL is also increasing.

Conclusions: Our unique findings emphasize that the detection of T-ALL and B-ALL by immunophenotypic analysis for better treatment and outcome of the patients and also trying to correlate the prevalence of T-ALL and B-ALL with economical status and also with other socio-demographic factors in study area.

Legal entity responsible for the study: Netaji Subhas Chandra Bose Cancer Research Institute

Funding: None

Disclosure: All authors have declared no conflicts of interest.

71P CALR mutations and their link with cellular calcium during megakaryocyte hyperplasia in MPNs

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Background: Megakaryocyte hyperplasia is a major characteristic of two myeloproliferative neoplasms (MPNs) known as essential thrombocythemia (ET) and Primary myelofibrosis (PMF). About 35% of ET and PMF patients harbour somatic *calreticulin* (*CALR*) mutations. CALR is a calcium (Ca^{2+}) buffering protein within the endoplasmic reticulum (ER). Ca^{2+} is an important element for megakaryocyte functions; however the impact of *CALR* mutations in cellular Ca^{2+} during megakaryocyte hyperplasia remains elusive.

Methods: *I-TASSER* software was used to study the aminoacid charge using the 3D structure of CALR mutant. Marimo cells and overexpressing CALR mutant HEK293T and DAMI cells were used as cellular models. CALR cellular localization was addressed by flow cytometry and confocal microscopy. Basal Ca^{2+} levels were measured by Fluo-8 staining. Furthermore cells were treated with Fendiline and BTP-2 calcium channel blockers to manipulate cellular Ca^{2+}.

Results: The present study shows that *CALR* mutations change the aminoacid charge of the Ca^{2+} binding region of CALR and that mutant CALR is localized outside the ER, within the cytoplasm and the cellular membrane. These results suggest that *CALR* mutations could be affecting the Ca^{2+} buffering activity within the ER. Therefore, we further analysed Ca^{2+} basal levels in CALR mutant cells, and our results showed that *CALR* mutations show lower cellular Ca^{2+}levels. These results lead us to think that low intracellular Ca^{2+} levels could be the driving force of megakaryocyte hyperplasia characteristic of ET and PMF. Therefore, we induced low intracellular Ca^{2+} levels in leukemic blast by using Ca^{2+} channel blockers and our results showed that treated cells display an increase of the megakaryocyte marker CD41a in the cell surface, suggesting an induction of megakaryopoiesis in these cells.

Conclusions: These findings elucidate that low intracellular Ca^{2+} caused by *CALR* mutations could be the driving force of megakaryocyte formation in ET and PMF. This study shows the relevance to understand the role of cellular calcium during megakaryocyte formation and this could unravel the pathogeny of CALR mutant in MPNs.

Legal entity responsible for the study: University of Salford

Funding: University of Salford

Disclosure: All authors have declared no conflicts of interest.

72P Approach based on magnetic nanocomplexes improves antitumor efficacy of dendritic cells immunotherapy in mice

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Background: Dendritic cell (DC)-based immunotherapy represents a promising approach for cancer treatment. However, the DC homing rate to the lymphoid tissues is poor, thus hindering the activation of antigen-specific T cells and reducing their antitumor efficacy. Here, we developed an approach based on magnetic nanoparticles (NP) to manipulate DC migration and thus elicit a more robust and efficacious antitumor response in tumor-bearing mice.

Methods: Mouse spleen DCs were loaded with nanocomplexes (NC) consisting of iron oxide NP ($8x10^{-12}$ g/cell) and lyophilized tumor tissue. To investigate the presence of NP in DCs, the method of $Fe2^{+}$ and $Fe3^{+}$ detection by Prussian Blue Staining was used. DCs were injected intradermally into tumor-bearing mice three times in an amount of $2x10^{5}$ per mouse at an interval of 3 days starting from day 7 after Lewis lung carcinoma inoculation. One group of mice that received DCs loaded with NC was exposed to a magnetic field for 1 h. The number and volume of metastases and tumor weight were assessed 28 days after tumor inoculation. At the same time, the levels of INF-γ, IL-10, TGF-ß, IL-4, FoxP3 mRNA expression in the spleen and inguinal lymph nodes were determined.

Results: The iron oxide NP showed no toxic effects on the DCs and had no effect on their viability. We found that almost all DCs are able to incorporate magnetic NP after 24h of incubation. Fewest metastases were found in the mice that received DCs loaded with NC and were exposed to a magnetic field: the number of metastases in mice from this group was 1.7 times less than in control mice. It should be noted that the volume of metastatic nodes in the lungs and the mass of the primary tumor were practically the same as in the control mice. The most pronounced decrease in FoxP3 mRNA levels in the lymph nodes, indicating a decrease in the activity of regulatory T cells, was also noted in the mice receiving DCs loaded with nanocomplexes and exposed to a magnetic field. In the mice of this group, a significant decrease in the level of IL-4 in the spleen was detected.

Conclusions: Our results suggest that an approach based on magnetic NC could be a promising strategy for improving the antitumor efficacy of DC-based immunotherapy.

Legal entity responsible for the study: National Cancer Institute of Ministry of Public Health of Ukraine

Funding: None

Disclosure: All authors have declared no conflicts of interest.

75P Signs of tumor-specific immune processes in the regression of large rat tumors under the influence of low-intensity EMR EHF and magnetite nanoparticles

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Background: The problem of elaboration of methods for effective mobilization of immune antitumor processes remains urgent. Earlier, it was shown that regression of experimental animal tumors can be achieved under the influence of low-intensive electromagnetic radiations (EMR) and magnetite nanoparticles (NPs) (Garkavi L.H. et al, 1996; 2013).The aim of the study was to determine the possibility of regression of large transplanted tumors of white rats under the influence of low-intensity EMR of millimeter range (EHF) and magnetite NPs.

Methods: In experiments on 123 white outbred male rats (200-300g) with transplanted Pliss lymphosarcoma - low-intensity EMR EHF (42.2 GHz, 10 mW/cm^2, exposure 15-30 min, low-frequency modulation) and magnetite NPs (10 ± 2 nm) in the form of the magnetic fluid AM-01 ("AM-Cube", Ekaterinburg) were used. The EMR acted on the animal's head starting 3 days before the tumor was transplanted. NPs were injected into peritumoral zone 2-3 times a week in a single dose of 17.7 mg/kg to animals with already formed tumors. Duration of treatment was 4 weeks. We studied the dynamics of tumor size, histochemical and cytometric changes in tumor tissue. The Wilcoxon test was used to evaluate the results.

Results: When EMR EHF was used, complete regression of tumors with a size of 5-6 cm^3 and a partial regression (by 30-40%) of tumors with a size of 10-13 cm^3 were noted. The effect was obtained in 33% of the animals. In cases of using of magnetite NPs, tumor regression was observed in 40% of the animals, complete regression of tumors with a size of 5-30 cm^3 was observed. Before the regression began, the tumor growth rates did not differ from those in the control group when using as one as the other factor. In addition, the regression was characterized by a rapid rate (5-7 days) and no signs of intoxication in animals. In the peritumoral area considerable macrophage activity and increasing number of cytotoxic T-lymphocytes were noticed.

Conclusions: The timing of the onset of regression, its dynamics and the absence of signs of intoxication during rapid elimination of large tumors indicated the deployment of antigen-presentation processes and specific killing of tumor cells by inducing apoptosis.

Legal entity responsible for the study: Rostov Research Institute of Oncology, Ministry of Public Healthcare of the Russian Federation

Funding: Rostov Research Institute of Oncology

Disclosure: All authors have declared no conflicts of interest.

76P Stimulation of RAC1/PAK1 signalling upregulates DNA damage repair genes via the BCL6/STAT5-switch

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Background: Colorectal cancer is one of the most prevalent types of cancer worldwide. The GTPase RAC1 and its effector PAK1 have been found overexpressed or hyperactivated in this type of cancers, particularly those with more aggressive and invasive features, which is frequently correlated with resistance to chemotherapeutics and unfavourable clinical prognosis. Previously, we described a new signalling pathway in

which activation of RAC1/PAK1 signalling promotes a transcriptional switch between the BCL6 repressor and the STAT5 transcriptional activator at a restricted subset of gene promoters.

Methods: Here we used a novel combinatory ChIP-Seq approach for the genome-wide identification of the BCL6/STAT5-switch target genes.

Results: Ontological enrichment analysis among the identified target genes revealed an overrepresentation of genes involved in DNA damage repair. Using the comet assay as readout for the extent of DNA damage, we show that the activation of RAC1/PAK1 signalling significantly accelerates DNA damage repair through the upregulation of pivotal genes.

Conclusions: This work highlights an additional role for the RAC1/PAK1 signalling axis that may contribute to the chemoresistant phenotype of aggressive colorectal tumours.

Legal entity responsible for the study: Paulo Matos

Funding: Fundação para a Ciência e Tecnologia.

Disclosure: All authors have declared no conflicts of interest.

77P Deciphering the regulation of the metastasis suppressor, NDRG1 in different cancer-types and its functional implications

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Background: The metastasis suppressor, N-myc Downstream Regulated Gene-1 (NDRG1) inhibits metastasis in a variety of cancer-types, including cancers of the breast, colon, pancreas and prostate. Its potent anti-oncogenic effects were demonstrated in multiple *in vitro* and *in vivo* studies, making it a promising therapeutic target. However, exactly how NDRG1 is regulated in different cancer-types and how different regulatory mechanisms affect NDRG1 function remain to be elucidated. Notably, post-translational modifications (PTMs), phosphorylation and cleavage of NDRG1, have been associated with its function. Therefore, it was crucial to examine whether these PTMs occur universally or selectively in different cancer-types. Further, considering the DNA repair role suggested for nuclear NDRG1, the effects of the above PTMs on nuclear NDRG1 levels was examined.

Methods: DU145 and PC3 prostate cancer cells, PANC-1 pancreatic cancer cells, HT-29 colon cancer cells, HepG2 and Hep3B hepatocellular carcinoma (HCC) cells were utilised. Full-length (FL) and truncated (T) NDRG1 isoforms were detected using a C-terminus directed antibody. The FL isoform was detected using an N-terminus directed antibody. Ser330 or Thr346 phosphorylation (p-NDRG1) was detected using specific antibodies.

Results: For the first time, we demonstrated that phosphorylation and potential cleavage of the NDRG1 protein occurs in all the various cancer cell-types examined. Although the levels varied, both the FL and T NDRG1 and its phosphorylated form were detected in all tumour cells assessed. The FL NDRG1 isoform was predominantly found in the cell nucleus. Ser330 p-NDRG1 was also highly localised in the cell nucleus, while Thr346 p-NDRG1 was mostly cytoplasmic. These cellular distribution patterns were similar in all cancer-types tested.

Conclusions: This study demonstrates for the first time that the NDRG1 protein is phosphorylated and potentially cleaved in diverse cancer cell-types. Further, FL NDRG1 and Ser330 p-NDRG1 were highly localised to the cell nucleus. These results indicate that the N-terminus region and phosphorylation at Ser330 could be crucial for nuclear expression and the well-known anti-metastatic function of NDRG1.

Legal entity responsible for the study: The University of Sydney

Funding: The University of Sydney, Cancer Institute New South Wales National Health and Medical Research Council, Cancer Australia, Cure Cancer Australia Foundation.

Disclosure: All authors have declared no conflicts of interest.

78P Registration-based automated lesion detection and therapy evaluation of tumors in whole body PET-MR images

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Background: Integrated PET/MR scanners can simultaneously acquire whole body functional PET data together with morphological and functional MR data. Whole-body PET-MRI datasets contain huge amounts of spatially detailed morphological, functional and metabolic information. We propose a method, based on deformable registration to a whole-body atlas, for computer aided detection of lesions in image data from an integrated PET-MRI system.

Methods: Images were acquired using an integrated 3T PET-MRI system (Signa PET/MR, GE Healthcare). Fat and water MR images were collected using a Dixon MR Attenuation Correction (MRAC) sequence (TE 1.67ms, TR 4.05ms, voxel size: 2x2x5.2 mm). Subjects underwent a PET scan after injection of [F18]-FDG (2 MBq/kg) with 3 minutes per bed, with a 100-120 minute interval between injection and scan start. PET reconstruction was performed using GE's fully 3D Time-of-Flight iterative reconstruction (2 iterations, 28 subsets, standard 5 mm filter, voxel size 3.125x3.125x2.78). Deformable image registration was used to spatially align subjects to a previously created morpphological and functional whole-body imaging atlas (Ekström et al., ISMRM 17), to allow voxel-wise comparisons between the imaged subjects and the atlas. Each voxel in the atlas contains mean and standard deviation of the PET uptake. Utilizing the knowledge that low ADC-values (low diffusion measured by MRI) and high FDG uptake (high metabolism measured by PET) is indicative of malignancy, suspected lesions can be detected by measuring how much the FDG uptake in each voxel deviates from "normality", as defined by the atlas. This approach generates a voxel-wise "lesion probability map" for the imaged subject. The same registration approach can be used to quantify longitudinal changes in detected lesions, for treatment evaluation.

Results: Lesion probability maps have been generated for patients with manually identified lesions, correctly assigning high values to the regions manually identified as suspected lesions.

Conclusions: The proposed method is promising for lesion detection in whole body PET-MRI images. Future work includes quantitative verification of the accuracy of the detected regions, comparing against manual detection by a radiologist.

Legal entity responsible for the study: Uppsala University

Funding: Antaros Medical

Disclosure: H. Ahlström, J. Kullberg: Co-founder and owner of Antaros Medical.

All other authors have declared no conflicts of interest.

79P 1,3,5 s-triazine containing analogues a prime Src family inhibitor: Design synthesis docking, anticarcinoma and angiogenic inhibition efficacy on cancer grafted CAM

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Background: The importance of angiogenesis for solid tumor growth is well recognized and evident by the vast differential of research devoted to the subject for over thirty years. It is a complex process directed by growth factors, receptors, extracellular matrix (ECM)-to-cell and cellto- cell interactions. Tyrosine kinase (TKs) is the protein enzymes catalyze the transfer of a phosphate group from an ATP molecule to a tyrosine residue of the target protein, thus leading to signal transduction. Cytoplasmic TKs such as Src, Abl and Lck have been to date discovered and characterized and found that inhibition signalling pathway. A special Src protein like FAK is a non-receptor protein-tyrosine kinase which have vital role in various cellular function like cytoskeleton reorganization, migration, adhesion, spreading, configuration and destruction of FA, cell protrusions, progression, proliferation and apoptosis. The functional ateration of Src signal may be the reason for cancer and metastasis. So this can predict that Src and their signal inhibition can utilized in cancer therapy. Triazine containing hybrid analogues act as a prime skeleton to inhibit Src family TKs like FAK so in present project we constructed 1,3,5-triazine containing analogues (TCA) as an effective cancer induced angiogensis inhibitor.

Methods: TCA analogues constructed accordingly similarity field positioning and pattern through forge V10. Further more *in-silico* simulation was done using autodock for most prominent analogues. The analogues derived via multifactorial synthetic protocol. The activity evaluation proceeded via *in-vitro* assay against MCF-7 (Breast cancer) cell line and further *in-ova* antiangiogenic potency evaluated against cancer induced chick chorioallantoic membrane.

Results: The newly designed and constructed TCA heterocycles expressed more than 56% of similar field point pattern and intra atomic alignments. The prominent pattern showed by the analogue 8d (chloro-anilino) and 8k (bromo-anilino). *In-silico* docking on hydrophobic site of Src family protein (PDB: 4BRX) revealed that analogue 8d have binding with CYS502, TR503, GLU506, ILE428, ASN551 while analogue 8k shoed interaction with THR503, GLU506, ILE428, LEU567, ASN551 amino acid residue which was similar like vendatinib. Biological evaluation showed that analogues 8d and 8k have great tendency to inhibit cancer induced angiogenesis with marginal toxicity profile.

Conclusions: We have developed a significant series of anticancer analogues and propound the site of binding on the surface of Src family TKs receptor FAK.

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Disclosure: All authors have declared no conflicts of interest.

81P A new isoquinoline alkaloid bersavine as a possible anticancer agent

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Background: Plants have had crucial role in the folklore of ancient cultures for over 5000 years. In addition to the use as food or spices, plants have also been utilized as medicine. Two remaining living traditions, the traditional Indian and Eastern medicine, have contributed most to the current state of knowledge related to medicinal plants. In their folklore, herbal medicines were prepared e.g. as teas or tinctures. These products are used as complementary treatment alongside conventional drugs till today. Another trend begun in the early 19th cent., which involved the isolation of active compounds from plants. This tendency led to the discovery of the analgesic alkaloids morphine and codeine or the cardiac glycoside digitoxin. Recently, a new alkaloid bersavine was isolated from *Berberis vulgaris*, along berbamine and berberine.

Methods: The dried root bark from *Berberis vulgaris* was minced and extracted with EtOH. The extract was evaporated, dissolved in HCl and extracted with nonpolar solvent. After the second extraction column chromatography on Al_2O_3 was performed. Subsequently was executed preparative TLC, which reveal a yet unknown alkaloid, later identified by MS and NMR analysis and named bersavine. Effect of bersavine on viability and proliferation was evaluated by WST assay and Trypan blue staining. Next was analysed its impact on cell cycle and apoptosis using the flow cytometry, activity of caspases and Western blot analysis of regulatory proteins was implemented.

Results: Bersavine's effect on cancer cells was first evaluated on panel of 9 different cell lines. Cancer cell lines MOLT-4, Jurkat, HT-29, HeLa and MCF-7 appear to be the most sensitive to the effect of bersavine. Follow-up experiments revealed that bersavine reduced cell viability and proliferation in a dose dependent manner within 24 h of treatment. Moreover, the reduction of cell viability was even more pronounce 48 h following the treatment. The decrease in cell viability was caused by the induction of apoptosis and activation of caspases.

Conclusions: All acquired results suggest that bersavine has very promising activity and it would be worthwhile to subject it to further evaluation.

Legal entity responsible for the study: Charles University, Faculty of Medicine in Hradec Kralove

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82P Tactics of surgical treatment of tumors of the sacrum

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Background: Tumor lesions of the sacrum are relatively rare and account for 1-7% of all spinal tumors. Tumors of this localization are usually detected when the tumor reaches a significant size and causes gross neurologic disorders and impaired pelvic organs. Radicality of removal of tumors of the sacrum depends on the involvement of the cauda equina, pelvic organs and vascular structures in the process.

Methods: The study involved 13 pateintd TMA clinic on the basis of the Department of Traumatology, Orthopedics, Neurosurgery with GPH No2 from 2011 to 2016. There were 6 women, 7 men. Age category ranged from 17 to 50 years. 1-stage: Holographic selective angiography by Seldinger's method of small pelvic vessels with subsequent embolization of "feeding" tumor of vessels. In addition, the anatomical features of the arteries are determined taking into account the localization of the tumor process, which is important in the operation. 2-stage: After preoperative embolization, three patients underwent hemisakrumectomy with VS3-VS5, and three patients underwent VS1-VS3 sarcomectomy. In this case, patients were additionally stabilized by TPF systems by Lumbo-Pelviofixation.

Results: In 2 cases during surgery, the tumor was intimately soldered to the roots of the horse tail and their isolation led to traumatization of the horse's tail, resulting in a postoperative delay in urine and stool. These violations were resolved within 2 months. In 4 patients with neurinoma S1, S2, S3 spine, an involuntary resection of these roots was performed. In these cases complications from the pelvic organs were not observed due to the presence of a cross innervation. In 2 patients, because of the duration of the operation, suppuration of the operating wound was noted with subsequent secondary healing. There were no lethal outcomes among 13 patients during follow-up.

Conclusions: The tactics of surgical treatment of sacral tumors, including the preliminary embolization of "feeding" arteries with subsequent radical removal of volume formation, reduces the risk of intraoperative complications, and also allows to remove the tumor totally, which in turn prevents its recurrence.

Legal entity responsible for the study: Traumatology Department

Funding: None

Disclosure: All authors have declared no conflicts of interest.

83P The impact of co-culture of NSCLC tumor cells and fibroblasts on drug response

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Background: The role of stromal cells and the tumor microenvironment has been described to modulate cancer development and tumor drug sensitivity, in part due to the interaction with fibroblasts. Therefore, it is critical to incorporate this feature in our in vitro model and to evaluate its potential impact in early stages of drug development.

Methods: Non Small Cell Lung Cancer (NSCLC) tumor cell aggregates were microencapsulated in alginate capsules, alone or in combination with fibroblasts (immortalized normal and cancer-associated fibroblasts – NFs and CAFs, and human dermal fibroblasts - hDFs), cultured during four weeks; and tumor growth and drug response, both *in vitro* and *in vivo*, were evaluated.

Results: Microencapsulation of H1650 and H1437 spheroids in mono- or co-cultures with fibroblasts resulted in viable cultures with tumor aggregate increasing continuously during culture time. However, tumor growth in in vitro co-cultures was dependent on the source of fibroblast and cell line used. When challenged with drugs, co-cultures with fibroblasts in our in vitro 3D model presented, in general, lower sensitivity to therapy after 3 weeks of treatment. H1437+hDFs co-cultures showed less sensitivity to volasertib treatment, with higher DNA concentration (2-fold higher versus mono-cultures) and higher resazurin reduction activity (35% versus 22% in mono-cultures). H1650+NFs co-cultures also demonstrated lower sensitivity to erlotinib and docetaxel treatment, with higher resazurin reduction activity (71% versus 29% in mono-cultures) and higher viable area of aggregates, respectively. Mono and co-cultures can also be injected in mice for the generation of xenografts. Evaluation of tumor growth based on the local of injection, fibroblast source and drug response was compared. In agreement with the in vitro results, only co-culture of H1437+hDFs injected in the lungs significantly enhanced in vivo tumor growth. However, co-culture of H1650 with fibroblasts did not result in altered tumor growth in vivo.

Conclusions: Altogether, we established a 3D model with co-culture of NSCLC tumor cell aggregates and fibroblasts that, depending on the pair used, presented reduced sensitivity to standard of care drugs, better reflecting the clinical observations.

Legal entity responsible for the study: iBET/ITQB-UNL; AbbVie and Oncotest

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Disclosure: All authors have declared no conflicts of interest.

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BIOMARKERS

84PD Relationship of PD-L1 and a T-cell inflamed gene expression profile (GEP) to clinical response in a multicohort trial of solid tumors (KEYNOTE [KN]028)

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Background: Antibodies targeting the PD-1 pathway have shown durable clinical benefit in multiple cancers. In the KN028 trial, the antitumor activity and safety of pembrolizumab were investigated in 20 solid tumors. Associations between PD-L1 expression and a T-cell inflamed GEP with response to anti-PD-1 therapy were also evaluated.

Methods: KN028 is a nonrandomized, phase 1b multicenter trial in patients with PD-L1 positive (≥1%, modified proportion score or interface pattern, QualTek IHC) advanced solid tumors treated with pembrolizumab 10 mg/kg Q2W for ≤2 y or until confirmed progression/unacceptable toxicity, death or withdrawal of consent. Response was assessed every 8 wk for 6 mo then every 12 wk. The primary endpoint was ORR (RECIST v1.1, investigator assessment [INV]) in patients who received ≥1 dose of pembrolizumab and had measurable disease. Secondary endpoints included safety, PFS and OS. ORR by central radiology review (IRC). Exploratory endpoints included relationships between GEP score (FFPE extracted RNA analyzed on NanoString nCounter) and PD-L1 expression levels (combined positive score, Dako IHC) with ORR and PFS. Data cutoff date was Feb 20, 2017.

Results: In the total study population (N = 475), there were 66 responders among 471 evaluable patients. ORR (95% CI) by INV ranged from 4.2% (0.1, 21.1) to 33.3% (15.6, 55.3) in 19/20 tumor types; no responders were observed in pancreatic carcinoma. ORR >10% was observed in 13/20 types (58/66 responders). ORR (95% CI) by IRC ranged from 4.3% (0.1, 21.9) to 26.3% (9.1, 51.2) in 18/20 tumor types. Treatment related AEs occurred in 65.5% of patients (14.1% grade 3-5). PD-L1 expression ($p = 0.034$) and GEP ($p = 0.012$) were associated with ORR in meta-analysis across tumors. Data for PFS, OS and relationships between PD-L1, GEP and MSI status with ORR will also be presented.

Conclusions: Pembrolizumab demonstrated favorable responses and manageable toxicity in the majority of the tumor types in KN028. Both PD-L1 and GEP score were predictive of clinical response, suggesting the utility of these biomarkers in selecting patients for immunotherapy and other novel therapies across a wide spectrum of tumor histologies.

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Legal entity responsible for the study: Merck & Co., Inc., Kenilworth, NJ, USA

Funding: Merck & Co., Inc., Kenilworth, NJ USA

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85PD Ultrasensitive detection of *EGFR* T790M mutation by droplet digital PCR (ddPCR) in TKI naïve non-small cell lung cancer (NSCLC) harboring *EGFR* mutation: Results of the nationwide program Biomarkers France of the French Cooperative Thoracic Intergroup (IFCT)

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Background: The presence of T790M mutation in *EGFR* accounts for nearly 50% of the acquired resistance to EGFR-TKIs. Earlier studies performed in small cohorts suggest that T790M was also detected in TKI-naïve NSCLC. Here, we use an ultra-sensitive ddPCR to address the incidence and clinical significance of T790M in a larger cohort of TKI-naïve NSCLC.

Methods: We analyzed 343 *EGFR* mutated patients of IFCT Biomarkers France program with available tumor DNA that were finally treated by EGFR-TKI. ddPCR™ was performed with QX200 system (BIO-RAD®, Hercules, USA). All samples were tested in duplicate. Colon cancers DNA were used negative controls.

Results: ddPCR identified a T790M mutation in 23/256 specimens (9%). T790M Fractional Abundance (FA) was ≥10%; ≥1% <10%; ≥0.1% <1%, ≥0.03% <0.1%, in 5 (22%), 7 (30%), 6 (26%) and 5 (22%) patients, respectively. The presence of a T790M mutation was not correlated with a specific type of *EGFR* mutations (exon 18, 19, 20 or 21). T790M positive and T790M negative populations were not different for clinical baseline characteristics. In a Cox model, a lower OS was associated with T790M mutated FA ≥ 10% (HR 18, IC95% 6-53, $p < 0.0001$) and 1≤FA<10% (HR 3.6, IC95% 1.6-8.2, $p < 0.002$). Median FA was 0.37, 0.48 and 1.87% for partial response, stable and progressive disease, respectively. The proportion of T790M mutations, is more frequent in patients with rapid (under 2 months)(n = 9/20, 45%) or usual median progression (12-14 months) (n = 8/20, 40%) compared to those with slow progression (more than 24 months) (n = 3/20, 15%)($p = 0.02$). In cases of rapid progression, T790M FA was over 1% in 7/9 (77%) patients.

Conclusions: Ultrasensitive detection of T790M is related in 9% of *EGFR* mutated TKI naïve NSCLC patients and has a negative prognostic value for T790M FA over 10%.

Clinical trial identification: NCT01700582

Legal entity responsible for the study: French Cooperative Thoracic Intergroup (IFCT)

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86PD Biomarker prevalence study and phase I trial of afatinib in children with malignant tumours

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Background: Dysregulation of the ErbB pathway may play a role in the development of paediatric neuroectodermal and mesenchymal tumours, suggesting that afatinib, an oral, irreversible ErbB family blocker, could be an effective treatment. A biomarker prevalence study assessed the frequency of ErbB-deregulations; in parallel, a Phase I trial (NCT02372006) was conducted.

Methods: Archived tissue samples from 277 neuroectodermal tumours and rhabdomyosarcomas were tested for protein expression of HER1–HER4, gene amplification of HER1/HER2 and mRNA expression of ErbB receptors and ligands. A Phase I afatinib trial in children aged 2 to < 18 years used a rolling 6 dose escalation design to determine the MTD/RP2D, starting at 18 mg/m^2/d (80% of the BSA-equivalent adult MTD dose), increasing to 23, 29, and 35 mg/m^2. PK was analysed after 1st dose and at steady state. Anti-tumour activity was assessed as per disease standards.

Results: In the biomarker prevalence study, ErbB deregulation markers were defined as: (A) HER1 gene amplification: HER1/Cen7 $\geq$2.0; $\geq$10% of cells with $\geq$15 copies; $\geq$40% of cells with $\geq$4 copies; or gene cluster in $\geq$ 10% of cells; (B) HER2 gene amplification: HER2/CEP17 $\geq$2.0; Protein expression (membrane); (C) EGFR H-score >150; and (D) HER2 H-score >0. Patients (pts) with tumours positive for $\geq$2 markers (A–D) will be selected to enrich the trial expansion cohorts. In the Phase I trial, 23 pts were screened, 17 treated and 12 evaluable for MTD. 1/7 pts experienced DLTs at 18 mg/m^2 and 2/5 at 23 mg/m^2. DLT events were decreased appetite, diarrhoea, dehydration, hypernatraemia, hypokalaemia, cheilitis, rash. Diarrhoea (12 pts) and dry skin (6 pts) were the most frequently reported drug-related AEs. Exploratory PK analysis suggested that exposure at 18 mg/m^2 in children was in a similar range as in adults treated with 40 mg/d. 1 pt with ependymoma had stable disease for 8 treatment cycles.

Conclusions: Afatinib was tolerable in children, with a safety profile similar to adults. The MTD was established at 18 mg/m^2/d and resulted in drug exposure considered effective in adults. The biomarker prevalence study identified exploratory screening markers being used to enrich patient selection in the ongoing expansion cohort.

Clinical trial identification: NCT02372006

Legal entity responsible for the study: Boehringer Ingelheim

Funding: Boehringer Ingelheim

Disclosure: D. Frappaz: Advisory board: BMS. P. Varlet: Advisory board: Roche (Herby trial), Novartis (dabrafinib trial), Boehringer (afatinib trial), Nanostring Technologies. D. Hargrave: Payments for being part of an advisory board in relation to the development of afatinib in childhood cancer. S. Gallego: Advisory board: Loxo Oncology. M. Kieran: Advisory board for Afatinib but do not receive any funds or payments. M. Casanova: Advisory board: Boehringer Ingelheim Pharma GmbH & Co. KG, Roche, Lilly, Bayer, Loxo Oncology. A. Lahogue, S. Wind, B. Stolze, D. Roy, M. Uttenreuther-Fischer: Employee of Boehringer Ingelheim. B. Geoerger: Advisory board: Boehringer Ingelheim. All other authors have declared no conflict of interest.

87PD Prospective study assessing the expression of angiogenesis-related genes as markers of anti-VEGFR2 response in advanced renal cell carcinoma

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Background: Since different therapeutic alternatives are reaching the clinic, we need biomarkers to guide treatment decissions in advanced Clear Cell Renal Cancer. This study explores the tumor expression of angiogenesis-related genes as potential markers of anti-VEGFR2 response.

Methods: Through an observational prospective study carried by the Spanish Oncology Genitourinary Group (SOGUG) FFPE tumor samples were collected from 159 RCC patients. A nCounter® Custom CodeSets (NanoString Technologies) was designed to measure the expression of a selected set of genes involved in angiogenesis (n = 23), immune response (n = 5) and RCC mutational landscape (n = 4), together with 4 house keeping genes. This technology was successfully applied to 135 primary tumors (81% clear cell histology), 4 metastasis, and 10 normal kidney tissues from patients treated with anti-VEGFR2 therapy. The association between the expression of the genes and PFS and OS was analyzed through cox-regression. Data provided correspond to multivariable analyses adjusted for MSKCC prognosis group, RCC histology and age.

Results: The 135 patients studied had been treated with sunitinib (91%), pazopanib (7%) or sorafenib (1%); most in first line (98%) and the median PFS was 21.0 months (95%CI=14.5-27.4). The strongest associations found corresponded to *VEGFC*, *VEGFA*, *PDGFRA* and *FGF2*. The median expression of these genes in the tumors was 28, 1075, 14 and 25 counts, respectively. High expression of *VEGFC* was associated with poor PFS (HR = 4.13, 95%CI=1.47-11.59, P = 0.0071) and the opposite occurred for *VEGFA*, which conferred longer PFS (HR = 0.05, 95%CI=0.005-0.48, P = 0.0098). *PDGFRA* and *FGF2* were associated with poor PFS (P = 0.01 and 0.012, respectively). Regarding OS, high expression of *VEGFC* was associated with poor OS (HR = 6.18, 95%CI=2.03-18.77; P = 0.0013). No significant associations were found for other genes.

Conclusions: We propose that the basal tumor expression of VEGF isoforms influences the survival of the patients treated with anti-VEGFR2 drugs.

Legal entity responsible for the study: Spanish Oncology Genitourinary Group (SOGUG)

Funding: Spanish Oncology Genitourinary Group (SOGUG)

Disclosure: All authors have declared no conflicts of interest.

88P PALB2 reversion mutations in breast, prostate, and ovarian carcinomas

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Background: Like BRCA1/2, deleterious mutations in PALB2 underlie deficiencies in homologous recombination-based DNA repair (HRD) and can underlie sensitivity to platinum (Pt) therapies and PARP inhibitors (PARPi). BRCA1/2 reversion mutations have been widely reported to cause therapy resistance. We report analogous reversion mutations in PALB2 for breast, ovarian, and prostate carcinomas (Ca).

Methods: Comprehensive genomic profiling (CGP) of DNA ($\geq$50 ng) extracted from 114,200 samples, both solid tumors and heme malignancies, was performed using hybridization-captured, adaptor ligation-based libraries (mean coverage depth >600X) for up to 315 cancer-related genes. Samples were evaluated for substitutions, indels, copy number changes and rearrangements.

Results: PALB2 mutations were found in ~1-3% of breast, ovarian and prostate carcinomas. Of 744 samples (0.7% of total) with likely deleterious PALB2 mutations, 7 (0.9%) harbored multiple alterations with at least one predicted to be a reversion. Of these samples, 4 were breast Ca, 1 a prostate acinar adenocarcinoma, 1 a high-grade ovarian serous Ca, and 1 an ovarian carcinosarcoma. For 3 samples the availability of multiple tests indicated the acquisition of the predicted reversion mutation(s) over time. Several reversion mutation types were observed: missense (1), compensatory frameshifts (3), overlapping small indels (2), and a deletion likely to disrupt splicing (1)

that may lead to skipping of exon 4 and an in-frame deletion excising a frameshift mutation. Multiple reversion mutations were observed in 2 cases. Only 1/7 cases also showed disruption of BRCA1/2.

Conclusions: In addition to the commonly sequenced genes BRCA1/2, PALB2 mutation can lead to homologous recombination deficiency. As with BRCA, the acquisition of additional mutations predicted to restore at least some PALB2 function and thus potentially confer resistance to therapies dependent on HRD, can be observed in tumors such as breast, ovarian, and prostate carcinomas. CGP is a valuable tool to identify clinically significant, albeit rare, primary PALB2 mutations in BRCA-negative tumors as well as acquired secondary resistance mutations in patients who progress on Pt and PARP inhibitor based therapies.

Legal entity responsible for the study: Foundation Medicine

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89P Pan-cancer genomic analysis of MSI-H tumors reveals commonly altered pathways

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Background: Microsatellite instability (MSI) is a hallmark of mismatch repair (MMR) deficiency and can be attributed to alterations in MMR-related genes including *MSH2*, *MLH1*, *MSH6*, and *PMS2*. Although alterations in PI3K pathway genes have been reported in MSI-High (MSI-H) colorectal carcinoma (CRC), a comprehensive enrichment analysis of the genomic landscape in MSI-H and MSI-stable (MSS) populations across tumor types is lacking. To better understand the molecular signatures of MSI and investigate new avenues for therapeutic opportunities, we sought to define the genomic landscape of MSI-H tumors across cancer types.

Methods: Comprehensive genomic profiling of 395 cancer-related genes, including MSI status, was performed on ~70,000 tumors. To identify potential driver alterations enriched in MSI-H tumors, variants in regions likely to be affected by polymerase slippage were excluded.

Results: As expected, alterations in *MSH2*, *MHL1*, *MSH6*, and *PMS2* as well as MMR deficiency variants were enriched in MSI-H specimens regardless of tumor type. We confirmed that variants in PI3K genes were enriched in MSI-H tumors in CRC. Importantly, this was observed across all MSI-H tumors, with 57% of pan-solid MSI-H tumors harboring a PI3K pathway variant compared to 24% of MSS tumors. WNT pathway variants were also enriched specifically in MSI-H tumors, except for CRC, in which frequent *APC* variants in MSS resulted in WNT enrichment in MSS tumors. Together, 84% of MSI-H tumors have at least one PI3K or WNT pathway variant (compared to 48% of MSS samples). Finally, although *ERBB2* alterations occur in both MSS and MSI-H tumors, we found that *ERBB2* amplifications occur nearly exclusively in MSS tumors, while *ERBB2* missense mutations are enriched in MSI-H tumors.

Conclusions: The genomic landscapes of MSI-H and MSS tumors suggest that they acquire alterations in distinct pathways. MSI-H tumors appear to share signaling pathway alterations across diseases, suggesting that MSI-H tumors may be more molecularly similar to one another than they are to MSS tumors of the same disease histology. These data may provide new avenues for exploration of targeted therapies in MSI-H tumors.

Legal entity responsible for the study: Foundation Medicine Inc.

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90P Molecular feature and clinical use development of gene expression profile "TP53 signature" in early stage breast cancer

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Background: There have been reported many gene expression profile which can predict prognosis of early stage breast cancer. We have reported the *TP53* signature which can predict dysfunction caused by *TP53* gene mutation in transcriptome level, and the status defined by *TP53* signature can predict more accurate prognosis of early stage breast cancer compare to the status defined by *TP53* DNA sequence. Recently, *TP53* signature was reported as robust predictor of early stage breast cancer by meta-analysis (BMC Cancer,2015). The aim of this study is to make clear the molecular feature of poor prognosis group diagnosed by *TP53* signature and to make easy and quick diagnostic kit which can be used in clinical situation.

Methods: We have done RNA-seq analysis using Hiseq2500 (Illumina) and reanalyzed TCGA data of breast cancer to make clear molecular feature of poor prognosis group defined by *TP53* signature. We made simple diagnostic kit using nCounter (Nanostring technology). Using this simple diagnostic kit, we diagnosed 234 breast cancer sample as *TP53* signature mutant or *TP53* signature wild, and we proved robust prediction power of *TP53* signature for early stage breast cancer. We used RNA-seq data to compare prediction power of *TP53* signature to Mammaprint, OncotypeDX, *TP53* structural mutation.

Results: TP53 signature mutant group have structural mutation in genes, including BRCA1, BRCA2, Rb1 except for TP53, which function is gene repair. In addition, TP53 signature mutant group shows high expression of PD-L1, high mutation burden and high copy number alternation. Analysis of 190 stage I-II breast cancer patients shows TP53 signature by simple diagnostic kit using nCounter has strong prediction power compare to Mammaprint, OncotypeDX, TP53 structural mutation, and clinical factors.

Conclusions: We have developed *TP53* signature as diagnostic system for early stage breast cancer which is useful in clinical situation. Poor prognosis group diagnosed by *TP53* signature shows molecular features which overlap good response marker of immune-check point inhibitors.

Legal entity responsible for the study: Japan

Funding: None

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91P Potential biomarkers of response to DKK1 blockade with DKN-01 in combination with paclitaxel in advanced esophagogastric cancer (EGC) patients (pts)

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Background: Overexpression of DKK1, a modulator of canonical WNT signaling, is frequently seen in malignant tumors and is often associated with worse survival. Preclinical studies have shown that DKK1 can augment tumorigenesis by promoting angiogenesis as well as enhancing tumor-associated immunosuppression. In this Phase I trial, DKN-01 (a humanized IgG4 monoclonal antibody against DKK1) showed encouraging early efficacy signals when combined with paclitaxel (DP) in EGC pts (Strickler et al., GI ASCO 2017). We performed correlative studies of plasma biomarkers of angiogenesis and inflammation in these pts.

Methods: Blood samples were collected from 34 patients treated with DP at baseline, and then weekly for 4 weeks (w). Plasma biomarkers were measured by multiplexed array for angiogenesis (bFGF, PIGF/PGF, sVEGFR1, sTIE-2, VEGF, VEGF-C, and VEGF-D) and inflammation (IFN-g, TNF-a, IL-1b, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70 and IL-13) (Meso-Scale Discovery) and by ELISA for HGF and SDF-1a (R&D Systems). Biomarker changes were evaluated by Wilcoxon Sign-Rank test, and correlations with response using Kendall's test values and with survival using two-sided Wald test in the Cox regression.

Results: Six of 34 EGC pts in this subset analysis (18%) had a PR and 11/34 (32%) showed SD with preliminary median PFS and OS of 13.7w and 28.4w, respectively. DP treatment induced significant and sustained increases in plasma IFN-g, IL-8, VEGF-D and decreases in IL-10 (all $p < 0.05$). Transient increases in bFGF and PlGF and decreases in sTie2 were also observed. IFN-γ, IL-10, and VEGF-D correlated with overall response and change in target lesion size. Finally, OS was poor in pts with high IL-6, IL-8 and TNF-a (HR > 1 all time-points) and prolonged in pts with greater increases in IL-2 and VEGF-D after treatment.

Conclusions: Prospective plasma biomarker analyses showed that DP treatment changed biomarkers of systemic immunity and angiogenesis in EGC pts, and indicated potential associations between inflammation biomarkers and outcomes. These hypothesis-generating results will inform future prospective investigation of these plasma biomarkers as well as paired evaluation of tumor biopsies for this combination regimen.

Clinical trial identification: Clinical trial information: NCT02013154

Legal entity responsible for the study: Leap Therapeutics, Inc.

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92P Low expression of miR-20a-5p predicts benefit to bevacizumab in metastatic breast cancer patients treated within the TANIA trial

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Background: Biomarkers predicting response to a bevacizumab containing therapy in metastatic breast cancer (MBC) are of urgent need. MicroRNAs (miRNAs) are involved in regulation of angiogenesis and development of treatment resistance and could therefore provide predictive information.

Methods: Profiling of 754 miRNAs was performed in FFPE tumor samples from 58 MBC patients who received bevacizumab-containing first-line treatment (learning set). Based on median PFS patients were divided into responders (R) and non-responders (NR). Differentially expressed miRNAs between R and NR were selected and validated in a cohort of 57 patients treated with first-line chemotherapy without bevacizumab (control set), to exclude miRNAs providing prognostic information only. In the learning set a multivariate analysis including clinical and pathological information was performed. MiRNAs significantly associated with PFS were further validated in 203 patients treated within the TANIA phase III trial randomizing between chemotherapy plus bevacizumab and chemotherapy alone for two consecutive treatment lines in patients pretreated with bevacizumab in first-line.

Results: Low expression of five miRNAs (miR-9-5p, miR-20a-5p, miR-21-5p, miR-210-3p, and miR-224-5p) was significantly associated with longer PFS in the learning set. For miR-20a-5p ($P = 0.035$) and miR-21-5p ($P = 0.004$) this association remained significant in multivariate analysis. In the control set no correlation between expression of those five miRNAs and PFS was seen. In tumor samples from the TANIA trial, low expression of miR-20a-5p was also significantly associated with longer second-line PFS and longer OS in the bevacizumab arm (HR 0.60, 95%CI 0.37-0.89; $P = 0.012$ and HR 0.54; 95%CI 0.32-0.83; $P = 0.007$, respectively) but not in the chemotherapy only arm (HR 0.73, 95%CI 0.48-1.09; $P = 0.119$ and HR 1.01 95%CI 0.63-1.62; $P = 0.964$, respectively). For miR-21-5p no significant association with PFS or OS in both treatment arms was observed.

Conclusions: MiR-20a-5p expression in breast cancer tissue showed a promising predictive value for identifying patients deriving greater benefit from bevacizumab-containing therapy.

Legal entity responsible for the study: Richard Greil for the translational research project, Roche for the TANIA trial

Funding: Roche

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93P Characterization of a novel tumor-suppressor gene CHL1 at 3p26.3 in esophageal squamous cell carcinoma

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Background: The major histologic subtype of esophageal cancer, esophageal squamous cell carcinoma (ESCC), is one of the most common cancers and has been ranked as the sixth leading cause of cancer-related deaths in the world. Using human genome U133 Plus 2.0 GeneChip, we identified gene down-regulation of Cell adhesion molecule L1 like (*CHL1*) located at 3p26.3 in ESCC. We analysed its down-regulated expression, biological effects and prognostic significance in ESCC.

Methods: To determine whether the down-regulation of *CHL1* was associated with aberrant methylation. Methylation-specific PCR (MSP) was performed in ESCCs and their corresponding non-tumor tissues, as well as ESCC cell lines. Loss of heterozygosity status of *CHL1* was evaluated by fluorescence in situ hybridization (FISH). The effects of *CHL1* re-expression or knockdown were determined in proliferation, invasion and metastasis assay. *CHL1* target genes and related pathways were identified by protein mass spectrometry, co-immunoprecipitation (Co-IP), immunofluorescence (IF) and western-blot. Clinical impact of *CHL1* down-regulated expression was assessed in 287 patients with ESCC.

Results: The results showed that down-regulation of *CHL1* was significantly associated with allele loss (14/21) and promoter methylation (19/21; $P<0.05$) in 39 pairs of ESCC and their corresponding non-tumor tissues by using MSP and FISH. Biofunctional investigation of *CHL1* revealed that *CHL1* significantly decreased cell proliferation, G1-S cell cycle transition, invasion/migration abilities, and promoted xenograft tumor growth as well as lymph node metastasis in vivo. The anti-proliferation effect by *CHL1* was mediated through inducing cell cycle arrest at G1/S checkpoint by down-regulation of p21 and p53 and up-regulation of cyclin D1; the inhibiting metastasis role was by suppressing Epithelial-to-Mesenchymal Transition and F-actin formation which was the result of recruitment Merlin to cell surface expression by *CHL1*. After a median follow-up of 48.23 months, multivariate analysis revealed that patients with CHL1 protein down-expression had a significant decrease in overall survival. Kaplan-Meier survival curves showed that CHL1 down-regulated expression was significantly associated with shorter survival in patients with ESCC.

Conclusions: *CHL1* plays a pivotal tumor suppressive role in ESCC; its down-regulated expression is an independent prognostic factor of patient with ESCC.

Legal entity responsible for the study: Henan Cancer Hospital

Funding: None

Disclosure: All authors have declared no conflicts of interest.

94P The role of vitamin D receptor polymorphisms in predicting response to therapy in non-muscle invasive bladder carcinoma

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Background: Clinicopathological factors predicting for response to Bacillus-Calmette Guerin (BCG) treatment for non-muscle invasive bladder carcinoma (NMIBC) are well defined but there is a paucity of data on genetic factors. Vitamin D has been found to have immunomodulatory effects in pre-clinical bladder cancer studies. Various single nucleotide polymorphisms of the Vitamin D Receptor (VDR) gene has also been found to be associated with response to treatment for mycobacterium. In this study, we evaluated the predictive role of 3 VDR single nucleotide polymorphisms (SNP) in patients with NMIBC in assessing BCG immunotherapy outcome.

Methods: Peripheral blood DNA was prospectively obtained from 140 evaluable EORTC intermediate to high risk NMIBC patients, who underwent post-transurethral resection intravesical regimes of BCG or BCG with interferon alpha. 3 VDR SNPs commonly implicated in susceptibility to tuberculosis infections were evaluated using high resolution melt (HRM) analysis followed by DNA sequencing. Kaplan-Meier together with Log-Rank test and Cox regression methods were used to analyze the data.

Results: Genotype frequencies were similar between the NMIBC patients and controls in accordance to the Hardy Weinberg equilibrium. Mean follow-up time was 91.9 months. Overall mean time to recurrence and progression was 25.8 months and 47.0 months respectively. Kaplan-Meier analysis indicate that individuals carrying the VDR genotype rs1544410 A/G were significantly associated with lower recurrence-free survival rates after BCG therapy ($p = 0.007$). The VDR rs1544410 "A" allele frequency was found to be higher in patients with bladder cancer recurrences ($p = 0.01$). No association of VDR genotypes with progression-free survival was found.

Conclusions: Our findings suggest that polymorphisms in the VDR gene correlate with response to BCG therapy in NMIBC patients and further work should be performed to evaluate their utility as predictive markers of response to BCG immunotherapy.

Legal entity responsible for the study: National Healthcare group Domain Specific Review Board

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Disclosure: All authors have declared no conflicts of interest.

95P Gene signatures as potential predictive markers of response to neoadjuvant chemotherapy in ER+/HER2+ breast cancer patients

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Background: Chemotherapy (CT) combined with anti-HER2 drugs (H) is the treatment of choice for HER2+ early breast cancer (BC) patients (pts). However HER2+ tumors are clinically and biologically heterogeneous, and treatment response largely varies according to ER status. Predictive biomarkers are urgently needed in this context. We have recently developed a meta-dataset of clinical trials of neoadjuvant CT +/− H (trastuzumab, lapatinib, or both) in HER2+ BC pts annotated for gene expression, hormone receptor status and pathological complete response (pCR) rates. We have shown that a gene-signature (GS) of RB-1 loss-of-function (RBsig) seems to be predictive of response to neoadjuvant CT +/− H in ER+/HER2+ BC pts in this meta-dataset. Here we report the results of additional analyses aimed to evaluate RBsig's predictive value against 10 previously developed GSs in the subset of ER+/HER2+ BC pts.

Methods: The association of RBsig with pCR was evaluated in comparison with previously described GSs of: low ER signaling, p53 mutation, high PI3K pathway signaling, high expression of HER2 amplicon genes, PAM 50 and 5 immune-related GSs. For each GS, samples were classified as High or Low group using a previously described classifier. Odds Ratio (OR) performance was calculated using the ROCR (v. 1.0) package in R and plotted by forest plot using the survcomp (v. 1.24) package.

Results: RBsig and the HER2 amplicon GS were best at predicting response to neoadjuvant CT +/− H (211 pts; p:0.017). In the subgroup of pts treated with CT alone ($n = 94$), only the PI3K pathway GS was significantly associated with pCR (p:0.026).

In pts treated with CT + H (n = 117) only the HER2 amplicon GS significantly correlated with pCR (p:0.042). RBsig showed a similar trend in both these subgroups (p: 0.078 and 0.104, respectively) The immune GSs and PAM50 were not associated with pCR, independent of treatment received.

Conclusions: RBsig and HER2 amplicon GS are strongly associated with pCR in ER+/HER2+ tumors unselected for treatment. These results support the potential use of such GSs as predictive markers of response to CT +/−H in ER+/HER2+ BC pts. Validation studies are warranted.

Legal entity responsible for the study: Angelo Di Leo

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Disclosure: A. Di Leo: Consultant/Advisory Board: Novartis, Pfizer, Lilly. All other authors have declared no conflicts of interest.

96P Predictive biomarkers for adjuvant therapy in gastric adenocarcinoma

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Background: Gastric cancer is a common and lethal malignancy, killing over 700,000 people worldwide. Recurrence rates are high even in early stage disease, with 5-year overall survival being < 50% for stage II disease and above. Current guidelines for adjuvant therapy include 5-fluorouracil (5-FU) chemotherapy in combination with radiation. The aim of our study is to develop immunohistochemical biomarkers to predict response to adjuvant chemoradiation in patients with resected gastric cancer.

Methods: A tissue microarray composed of 100 specimens from primary resected gastric cancer cases was constructed. All patients received 5-FU based chemotherapy, and 92% of patients received radiation. Tumors underwent immunohistochemical staining for 11 proteins (HER2, EGFR, p-AKT, PTEN, MTOR, VEGFA, IGF1R, MLH1, MSH2, MSH6, PMS2), and H-scores were calculated. Primary endpoints were progression-free survival (PFS) and overall survival (OS). Survival analysis was performed by Kaplan-Meier method with log-rank test for assessing statistical significance. Multivariate analysis was performed with Cox regression.

Results: Mean follow-up time for the cohort was 39.4 months. Ninety-one of 100 cases had sufficient tissue for biomarker analysis. Interestingly, low expression of MSH2 and MSH6 was significantly associated with shorter PFS, while there was a trend towards worse OS for patients with low MSH2 expression. In multivariate analysis, adjusting for well-characterized prognostic variables, both MSH2 and MSH6 retained their predictive significance. In addition, nuclear expression of the tumor suppressor PTEN was associated with longer OS. No other biomarkers were significantly associated with PFS or OS.

Conclusions: These results indicate that low expression of MSH2 and MSH6 predicts for poorer outcomes in patients with resected gastric adenocarcinoma, independent of other predictive markers.

Legal entity responsible for the study: Hellenic Cooperative Oncology Group

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97P Large-scale DNA organization is a prognostic marker of breast cancer survival

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Background: Breast cancer is the leading cause of cancer-related deaths among women worldwide. Current clinicopathological parameters only partially encompass and predict biological diversity and therefore limit our ability to make informed treatment decisions and predict outcomes. The successful future of oncology will rely on our ability to correctly select patients who would benefit from chemotherapy or benefit from treatment intensification, and spare the rest from unnecessary exposure to toxic and expensive therapies. Tumour biology and prognostic markers may be the key to achieving the above goal. We investigated whether changes in Large scale DNA Organization (LDO) of tumour epithelial nuclei is an indicator of the aggressiveness of the tumour.

Methods: We tested our algorithm on a set of 172 TMA cores samples, coming from 95 breast cancer patients. Thirty five patients died of breast cancer and 60 were still alive 0 years after surgery. This TMA slide was stained with Feulgen-thionin and imaged using an high-resolution Imaging system. Automated segmentation of cell nuclei followed by manual selection of intact, in-focus nuclei resulted in an average of 50 cell nuclei per sample. Approximately 60 features measuring Large-scale DNA organization were calculated.

Results: Forward stepwise Linear Discriminant analysis selected 6 features that, combined linearly, gave the best discrimination between nuclei from alive patients specimens and nuclei from deceased patients specimens. Patient LDO score was defined as the percentage of cell nuclei with a high cell LDO. LDO algorithm correctly classified 82.1% patients, with a specificity of 79% and a sensitivity of 88%. Furthermore, individuals with a high LDO score had a 9x fold increase in relative risk of death. In the multivariate Cox regression model, LDO, Node status and Tumor Grade were all significant predictors of cancer death.

Conclusions: This data suggests that LDO could be used to identify patients more likely to have an aggressive disease and thus select a candidate for more aggressive or novel adjuvant therapies.

Legal entity responsible for the study: Martial Guillaud

Funding: None

Disclosure: All authors have declared no conflicts of interest.

98P Telomere associated variables and their potential in CLL prognosis

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Background: The molecular mechanisms that determine disease progression and evolution in CLL are not completely known. Telomeres are usually short in CLL and their attrition may contribute to disease evolution. In addition, telomerase activity (TA) levels have also been associated with prognosis and response to treatment. In order to integrate telomere associated variables (TAV) in CLL disease management further studies with robust methodology are required.

Methods: Purified peripheral CD19 (+) B-cells from 19 healthy donors and 42 CLLs in different stages of disease were obtained from the National Bank of DNA (Salamanca, Spain). Samples were tested to determine full telomere length (TL) distribution-including percentage of short telomeres by a high throughput quantitative fluorescence in situ hybridization (HT-Q-FISH) technique. TA by Quantitative Telomere Repeat Amplification Protocol (Q-TRAP) was also quantified. Full statistical analysis of the results in the context of the clinical history of the patients was performed.

Results: Data from the pilot, retrospective study stablished strong correlations between key CLL variables and the severity of the disease. Overall, TL was shorter and TA presented higher values compared to normal age-matched subjects. Interestingly longer TL was observed for all CLL patients with somatic hyper-mutation (SHM) that in turn, was associated with better prognosis. Concomitantly, TA was elevated in those patients with no SHM and was linked to poor response to treatment and negative prognosis. The percentage of short telomeres was significantly higher for Binet C/Rai III and IV cases.

Conclusions: The use of reliable technologies to measure TAV should be integrated during early diagnostic in CLL to enhance the ability to predict disease evolution. This will require larger, prospective, longitudinal clinical studies.

Legal entity responsible for the study: Life Length S.L.

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99P Micro-RNA profile in advanced metastatic breast cancer as a predictive tool for response to bevacizumab-paclitaxel

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Background: Bevacizumab-containing therapy improves progression-free survival (PFS) in human epidermal growth factor receptor (HER) 2-negative metastatic breast cancer (mBC), but its use has been questioned due to the lack of benefit in overall survival (OS). To date, biomarkers to predict its positive effect are not available. Interestingly, miRNAs have emerged as regulators of most processes, forming tight interconnected feedback loops with genes under their regulation. Currently, different analyses, such as microarray, are performed in order to identify miRNA biomarkers, using formalin-fixed and paraffin-embedded (FFPE) tissue samples.

Methods: In the present study we recorded clinical data from 57 mBC patients, and selected two (4 + 4) PFS extreme groups for the analysis of the miRnome. Three miRNAs were used for normalization (U6, 191-5p and 103-a-3p). miRNAs for model construction were selected by differential expression between the two groups. Candidates were

measured in the remaining 49 cases, and stepwise based Akaike criterion was used for profile generation. Additionally, integrative miRNA and mRNA analyses were done to reveal markers and pathways with potential clinical impact.

Results: We selected two groups of patients with extreme differences on PFS (2.48 ± 1.85 vs 35.43 ±8.03 months) for their miRnome study. The expression profiles of miRNAs in both groups were highly correlated, except for 13 miRNAs where statistical differences arised. These miRNAs were selected as candidates for profile generation on the 49 additional cases, and a combination of five of them (miR-362-3p, miR-150b-5p, miR-671-3p, miR-744-3p and miR-941) was able to accurately discriminate two PFS groups. Additionally, Kyoto Encyclopedia of Genes and Genomes (KEGG) analyses on miRNA possible target genes revealed interesting pathways to explore in these patients, such as cellular adhesion.

Conclusions: By combining experimental approaches and computational biology, we have identified candidate markers of outcome for bevacizumab-containing therapy. The five miRNAs included in the prognostic profile and cellular adhesion related genes should be explored as potential biomarkers.

Legal entity responsible for the study: Fundación para la Investigación del Hospital Universitario La Paz

Funding: None

Disclosure: All authors have declared no conflicts of interest.

100P Biomarkers of immune therapy in CUP

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Background: Carcinoma of unknown primary (CUP) accounts for approximately 3% of all malignancies. Identification of common cancer pathway alterations (hallmarks of cancer) in diverse cancer lineages offers a rationale for search for biomarkers of targeted therapies in patients with CUP. Avoiding immune destruction is a more recently recognized common cancer characteristic and biomarkers associated with immune checkpoint blockade were explored in this study.

Methods: 392 cases of CUP were tested with NextSeq platform with a 592-gene panel. Tumor mutational load (TML) was calculated using only somatic nonsynonymous missense mutations; microsatellite instability (MSI) was evaluated with NGS by direct analysis of known MSI loci in the target regions of the sequenced genes. ArcherDx FusionPlex Assay was used to detect gene fusions and 52 gene targets were analyzed for 156 tumors. IHC was used to detect tumor expression of PD-L1 (SP142 antibody) and PD-1 TILs (NAT105 antibody) All tests were done in a CLIA-certified lab.

Results: Average patient's age was 62.4 years; 52% were female. TML high was seen in 12.2% (48/392) tumors using a cutoff of 17 mutations/Mb. MSI-high was detected in 10/392 (2.6%) of tumors. A total of 70 different genes were found mutated with the incidence ranging from 0.3% to 54%; the most frequent were TP53 (53.5%), KRAS (21.5%) and ARID1A (14.6%). Additional notable targetable mutations include PIK3CA (13.1%), CDKN2A (8.1%), PTEN (4.5%), BRAF (4.1%), ATM (3.3%), NOTCH1 (2.4%) and ERBB2 (1.5%). Targetable gene fusions identified included FGFR2 fusions (N = 2), RET (N = 1), RAF1 (N = 1).Tumors with fusions identified carry a lower TML (average 5.9) than the complete cohort (11.7, $p < 0.001$) with no MSI-high seen in this subgroup. Tumor expression of PD-L1 was seen in 22.5% (82/365) tumors while PD-1 expression on tumor infiltrating lymphocytes seen in 58.7% (37/63). The highest frequency of gene amplification seen were CCND1 (4.7%), FGF3 (3.4%), FGF4(3.4%), FGF19(3.4%), Her2 (3.1%), MYC (2.9%) and AKT2 (2.4%). Of note, CD274 (PD-L1) was rarely amplified (1.4%).

Conclusions: Using a multiplex testing approach, 28% of CUPs had biomarkers (TML-H, MSI-H and/or PD-L1) of response to the immune check-point blockade were identified, making CUP one of the most likely candidate to benefit from immune checkpoint inhibitors.

Legal entity responsible for the study: Joanne Xiu

Funding: None

Disclosure: J. Xiu, Z. Gatalica: Employee of Caris Life Sciences.

101P A circulating TH2 cytokines profile predicts survival in patients with resectable pancreatic adenocarcinoma

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Background: Surgery is the only potentially curative option for patients with pancreatic ductal adenocarcinoma (PDAC), but metastatic relapse remains common. We hypothesized that the expression levels of inflammatory cytokines could predict recurrence of PDAC, thus allowing to select patients who most likely could benefit from surgical resection.

Methods: We prospectively collected plasma at diagnosis from two-hundred eighty-seven patients with pancreatic resectable neoplasms. The expression levels of 23 cytokines were measured in ninety patients with PDAC by using a multiplex analyte profiling assay.

Results: Levels higher than cutoff identified of the T_H2 cytokines interleukin (IL)4, IL5, IL6, of macrophage inflammatory protein (MIP)1a, granulocyte-macrophage colony-stimulating factor (GM-CSF), and monocyte chemoattractant protein (MCP)1, and of IL17a, IFN-γ- induced protein (IP)10, and IL1b were significantly associated with a shorter median OS. In particular, levels of IL4 and IP10 higher than cutoff identified, and level of T_H1 cytokines TNFa and INFg, and of IL9 and IL1Ra lower than cutoff identified were significantly associated with a shorter DFS. In the multivariate analysis, high IP10 was confirmed as negatively associated with OS (HR = 3.097, P=0.014) and IL4 and TNFa remain negatively (HR = 2.75, P=0.002) and positively (HR = 0.224, P=0.049) associated with DFS, respectively. Simultaneous expression of low IL4 and high TNFa identified patients with best prognosis (HR = 0.313, P<0.0001).

Conclusions: We demonstrated that, among a series of cytokines, IL4 is the most significant independent prognostic factor for DFS in resectable PDAC patients, and it could be useful to select patients with high risk of early recurrence who may avoid an unnecessary resection.

Legal entity responsible for the study: University of Verona

Funding: Associazione Italiana per la Ricerca sul Cancro (AIRC)

Disclosure: All authors have declared no conflicts of interest.

102P Analytic validation of a next generation sequencing assay to identify tumor mutational burden from blood (bTMB) to support investigation of an anti-PD-L1 agent, atezolizumab, in a first line non-small cell lung cancer trial (BFAST)

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Background: Recent data suggest that analysis of tumor mutational burden (TMB), a measure of tumor neo-antigenicity derived from tissue biopsies, has shown clinical utility in predicting outcomes for patients treated with anti-PDL1/PD1 therapies across a range of tumor types. Unfortunately, such analyses require quality tumor tissue that in many cases is not available for patients diagnosed in the metastatic setting. As such, there exists a significant unmet medical need for orthogonal diagnostic approaches that enable the analysis of TMB in patient samples without requiring tumor tissue. Herein, we describe the development of an assay to identify TMB from the circulating tumor DNA derived from blood (bTMB), and the analytical validation (AV) that supports its application in a phase III clinical trial in 1L non-small cell lung cancer comparing the anti-PD-L1 agent, atezolizumab, against standard of care platinum-based doublet chemotherapy (BFAST).

Methods: The bTMB assay delivers a count of somatic base substitutions down to 0.5% allele frequency across 394 genes from as little as 1% tumor content in a cell free DNA (cfDNA) sample. AV focused on establishing accuracy and precision, as well as the limit of circulating tumor DNA required to make precise and reliable bTMB calls. Accuracy of the two different bTMB cutoffs being evaluated in BFAST was established against an orthogonally validated TMB platform. Precision was evaluated by comparing the reproducibility of bTMB calls across replicate samples.

Results: The average PPA, NPA and PPV across both bTMB cutoffs was 95%, 100% and 100%, respectively. The average precision was 96%, with a coefficient of variation of 17% across all replicates. The assay limit of detection was defined as 1% tumor content in at least 20 ng of cfDNA.

Conclusions: We have developed and analytically validated a blood-based assay to determine bTMB with high accuracy and precision from as little as 1% tumor content in 20 ng of cfDNA. Clinical validation of bTMB will be established in a prospective, randomized phase III clinical trial, BFAST, with a primary endpoint of progression free survival.

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

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Disclosure: D. Fabrizio, C. Malboeuf, D. Lieber, S. Zhong, J. He, E. White, M. Coyne, J. Silterra, T. Brennan, J. Ma, M. Kennedy, D. Lipson, G. Otto: Employee and stockholder of Foundation Medicine. E. Schleifman, S.M. Paul, Y. Li, D.S. Shames, C.A. Cummings, E. Peters, M. Kowanetz: Employee and stockholder at Genentech.

103P Comparison of continuous measures across diagnostic PD-L1 assays using image analysis

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Background: Tumour programmed cell death ligand-1 (PD-L1) expression is a key biomarker in identifying patients who may have an enhanced response to non-small cell lung cancer treatment using anti-PD-1 (e.g. nivolumab and pembrolizumab) or anti-PD-L1 (e.g. atezolizumab and durvalumab). Each treatment is currently used in conjunction with an individual PD-L1 diagnostic immunohistochemistry (IHC) assay and it is unclear whether immunolabelling parameters determined by pathologists are comparable across assays. We extended previous studies (Ratcliffe et al Clin Cancer Res 2017; Ratcliffe et al ASCO-SITC 2017 [abstr 7]) by performing image analysis (IA) with a customised PD-L1 scoring solution to permit a quantitative comparison of the 4 PD-L1 IHC assays.

Methods: We developed an IA scoring algorithm that enabled us to quantify the percentage of positive tumour cells on a whole slide image for 4 PD-L1 assays (Ventana SP263, Ventana SP142, Dako 28-8, Dako 22C3). The analysis was applied to 473 commercially available NSCLC cases (180 cases with SP142). We co-registered the consecutive slides per case and harmonised tumour and exclusion annotations to ensure that readouts of identical areas were compared per case.

Results: In agreement with previous reports, IA results showed concordance between 3 assays, whereas the SP142 assay was discordant. Moreover, high correlation was observed between IA results and pathologist ratings. This correlation could be further improved by matching the information the pathologist received to the same information used in the IA solution: blinding against the assay, scoring on digital scans and masking of non-comparable image regions. The remaining differences represent the differing sensitivity profiles of the assay protocols.

Conclusions: The results of our objective IA suggest differences in sensitivity between the analysed assays. Importantly, despite the observed differences, we confirm previous findings indicating concordance between 22C3, 28-8 and SP263. In addition, our analysis provides a continuous distribution of PD-L1 measurements allowing deeper characterisation of the samples. Tobias Wiestler and Moritz Widmaier are joint first authors.

Legal entity responsible for the study: AstraZeneca PLC

Funding: AstraZeneca

Disclosure: T. Wiestler: Full-time employee Definiens, Stock/shareholder: Definiens/AstraZeneca. M. Widmaier: Full-time employee Definiens. J. Walker, C. Barker, M. Scott: Employee and shareholder AstraZeneca. F. Sekhavati, A. Budco: Employee Definiens. K. Schneider: Full-time employee Definiens AG. K. Steele: Employee MedImmune, shareholder AstraZeneca, Patents/Royalties MedImmune/AstraZeneca. M.C. Rebelatto: Employee AstraZeneca/MedImmune; Stockholder AstraZeneca/MedImmune.

104P Pharmacokinetics (PK) and pharmacodynamics (PD) of a novel carcinoembryonic antigen (CEA) T-cell bispecific antibody (CEA-CD3 TCB) for the treatment of CEA-positive solid tumors

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Background: CEA-CD3 TCB (RG7802, RO6958688) is a novel T-cell bispecific antibody targeting CEA on tumor cells and CD3e on T cells. In mouse models, CEA-CD3 TCB displays potent anti-tumor activity, leads to increased intratumoral T cell infiltration and activation and up-regulates the PD-L1/PD-1 pathway.

Methods: Biodistribution was assessed in mice using SPECT/CT. Patient (pt) samples were from 2 dose-escalation studies in CEA-positive solid tumors. Study 1 (S1): single agent weekly (qw) (0.052-600 mg IV; n = 80), and Study 2 (S2): CEA-CD3 TCB qw (5-160 mg IV) plus atezolizumab 1200 mg q3w (n = 46). Analytics: [CEA-CD3 TCB]—bifunctional PK assay; antidrug antibodies—ELISA; immunophenotyping in peripheral blood (PB)—flow cytometry (FCM), in baseline (BSL) and on-treatment (OT; week 7) biopsies by immunohistochemistry and FCM; plasma cytokines—multiplex assay; PD-L1—SP142 assay.

Results: In mice, CEA-CD3 TCB preferentially accumulated in CEA-positive tumors. CEA-CD3 TCB showed near-linear PK in both studies (S1: 35; S2: 28). In pts with matched BSL and OT biopsies, 7/10 CRC pts treated with $\geq$ 60 mg of CEA-CD3 TCB in S1 had > 2.4-fold increase in CD8 T cells, which did not correlate with RECIST response. In S2, 2/2 CRC pts receiving $\geq$ 80 mg of CEA-CD3 TCB (with RECIST reduction $\geq$ 25%), showed > 8-fold increase in CD8/Ki67 T cells. SUVmax decrease (FDG-PET) correlated with BSL levels of CD4-OX40 and CD8-PD1 in S1 and CD8-OX40 in S2. In PB at week 4, a > 4-fold expansion of activated CD8 T cells (HLA-DR/Ki67) but not CD4, was detected in most pts at doses $\geq$ 60 mg (S1: 24; S2: 9). In most pts, increases in IL-6 were seen after the first TCB infusion and in fewer cases after the second/third infusion in both studies (S1: 62; S2: 33).

Conclusions: On-treatment increases in intratumoral CD8 T cells consistent with the mechanism of action and support that CEA-CD3 TCB is the first tumor-targeted T cell bispecific showing biological activity. The activation level of intratumoral T cells at BSL could be a predictive biomarker of response. In preclinical models, tumor targeting has been demonstrated. Updated data will be presented. Clinical data are reported separately.

Clinical trial identification: NCT02324257

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

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105P Baseline gut microbiota in metastatic melanoma patients treated with ipilimumab: Relation with clinical response and colitis

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Background: It is now demonstrated that gut microbiota composition has a determining influence not only on inflammatory bowel diseases but also more broadly on the immunological status of healthy individuals as well as in patients with cancer. We explored the potential role of baseline gut microbiota in anti-tumor response and in intestinal toxicity of patients with metastatic melanoma treated with anti-CTLA4 mAb ipilimumab. Moreover we explored how the composition of gut microbiota could influence not only local gut-immunity but also distant sites such as anti-tumor immunity.

Methods: Fecal microbiota compositions were prospectively assessed at baseline and before each ipilimumab infusion, using 16S rRNA gene sequencing. Patients were further clustered based on microbiota patterns. Peripheral blood lymphocytes immunophenotypes were studied in parallel.

Results: A distinct baseline gut microbiota composition was associated with both clinical response and colitis. As compared to patients whose baseline microbiota was driven by *Bacteroides* (Cluster B), patients whose baseline microbiota was enriched with *Firmicutes* (Cluster A) had longer progression-free survival and overall survival. Most of the baseline colitis-associated phylotypes were related to *Firmicutes*, whereas no-colitis related phylotypes were assigned to *Bacteroides*. A low proportion of peripheral blood regulatory T cells was associated with Cluster A, long-term clinical benefit and colitis. Ipilimumab led to a higher Inducible T-cell COStimulator induction on CD4+ T cells and to a higher increase in serum CD25 in patients who belonged to Cluster A.

Conclusions: Baseline gut microbiota enriched with *Firmicutes* is associated with beneficial clinical response to ipilimumab and more frequent occurrence of ipilimumab-induced colitis.

Clinical trial identification: GOLD study: SC12-018; ID-RCB-2012-A01496-37

Legal entity responsible for the study: Coordination: Franck Carbonnel (AP-HP)

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106P The association between PD-L1 expression, EGFR mutation and ALK translocation in a series of 982 lung cancers

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Background: PD-L1 expression testing is mandatory prior to pembrolizumab prescription in non-small cell lung cancer. Pembrolizumab was made available in the UK through the Early Access to Medicines Scheme (EAMS) in May 2016 and was NICE-approved in December 2016. Our Molecular Pathology Diagnostic Service has been offering PD-L1 testing using Dako's 22C3 IHC assay in parallel with EGFR and ALK testing. We present here data on the relationships between PD-L1 expression, and EGFR and ALK status in a series of 982 tumours.

Methods: PD-L1 expression testing was performed using the aforementioned assay on the 4800 Dako stainer. EGFR mutation testing was performed using the Therascreen kit on the RGQ platform and using COBAS kit (both screening for exon 19 deletions, L858R, G719X, L861Q, S768I, exon 20 insertions and T790M); ALK translocation was assessed using the D5F3 Ventana antibody on XT platform. PD-L1 was considered positive when more than 1% of tumour cells showed membranous staining.

Results: Of the 982 tumours, 492 were positive for PD-L1 (50.1%), 85 bore EGFR mutations (8.7%) and 14 bore ALK translocations (1.4%). There was no significant difference in PD-L1 expression rate with EGFR mutation status. However, whereas 39.3% tumours with a classical EGFR mutation were PD-L1 positive, 86.4% with a rare EGFR mutation (G719X, L861Q, S768I, exon 20 insertions) were PD-L1 positive ($p = 0.0006$). PD-L1 positivity rate was 52.3% and 85.7% in ALK non-rearranged and rearranged tumours, respectively ($p = 0.01$).

Conclusions: Our data show that the presence of classical or of rare EGFR mutations is associated with different degrees of PD-L1 expression, which may have future therapeutic implications. Our data also show that the presence of an ALK translocation is positively associated with PD-L1 expression.

Legal entity responsible for the study: N/A

Funding: None

Disclosure: All authors have declared no conflicts of interest.

107P Association of tumor and stroma PD-1, PD-L1, CD3, CD4 and CD8 expression with response to nivolumab treatment in NSCLC patients

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Background: PD-L1 immunohistochemistry (IHC) correlates only moderately with response to nivolumab treatment. Characterizing PD-1, PD-L1 and T-cell markers in both tumor and stroma might improve the predictive value of tissue IHC as predictive biomarker in this setting.

Methods: From 08-2015 to 12-2016 patients with stage IV NSCLC treated with nivolumab were registered and prospectively followed. A histological tumor biopsy, obtained before start of nivolumab, was required. Tumor PD-L1 expression and immune cell (IC) PD-L1, PD-1, CD3, CD4 and CD8 expression in tumor and stroma was assessed using IHC on serial sections. IC infiltration was scored semi-quantitatively indicating no, very low, low, intermediate, or high infiltration. Presence of CD4+ macrophages in between tumor cells was used to aid assessment of tumor PD-L1 expression. Nivolumab was dosed 3 mg/kg Q2W and response assessment was done by CT every six weeks.

Results: Overall response rate of pts ($n = 65$) was 23% and quantifiable ($\geq$1%) tumor PD-L1 expression was found in 25% of pts, versus <1% expression in 75% of pts. Univariate analyses showed a significant correlation between the levels of tumor PD-L1 expression (0%, 1-50%, >50%) and associated response rates of 17%, 22% and 57% respectively. Stromal IC expression of PD-L1, CD3, CD4 and CD8 also correlated with response ($p < 0.05$ for all markers). CD8+ tumor IC infiltration and stromal PD-1+ staining did not correlate with response. In the subgroup of $n = 47$ pts with negative (<1%) tumor PD-L1 expression, pts with either high CD3 or high PD-L1 stromal IC expression ($n = 45$) showed a remarkably high response rate of 59% ($p = 0.009$).

Conclusions: A clear positive correlation was found between PD-L1 expression and response. The distribution of PD-L1 expression was lower compared to historical data. Availability of CD4 IHC that identified PD-L1 positive macrophages is the explanation for lower percentage of tumor PD-L1 positive samples. Stromal PD-L1, CD3, CD4 and CD8 IC expression were all predictive for treatment response. In tumor PD-L1 negative pts, high stromal PD-L1 and/or CD3 IC expression selected pts with a remarkably high response rate.

Legal entity responsible for the study: A. J. de Langen

Funding: VU University Medical Center, Department of Pulmonology

Disclosure: All authors have declared no conflicts of interest.

108P Characterisation of heterogeneity in microsatellite instable (MSI) tumours associated with distinct cell types and immune phenotypes

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Background: In the immunotherapy era, a better understanding of heterogeneity in MSI cancers is required. We evaluated gene expression profiles of MSI colorectal (CRC), gastric (GC) and endometrial cancer (EC) samples with our cell-of-origin signature (CRCassigner), which is able to classify samples in differentiated (goblet-like; CMS3), differentiating (transit-amplifying – TA; CMS2) and less differentiated/mesenchymal (stem-like; CMS4 and inflammatory; CMS1) subtypes to identify whether MSI transcriptional heterogeneity exists.

Methods: Normalised RNAseq/microarrays gene expression profiles and microsatellite status were downloaded from TCGA. CRCassigner classification of samples was performed using Pearson correlation. Samples with low classification confidence were classified as "mixed" subtype. Gene selection enrichment analysis (using published immune markers) and differential protein expression analysis (of PDL1 from Cancer Proteome Atlas data) was performed between inflammatory and goblet-like MSI samples.

Results: The majority of MSI-H in all the 3 cancer types expressed the inflammatory profile. While in MSI-H CRC only two subtypes were present (inflammatory - 91% and goblet-like - 9%), 5 subtypes in MSI-H GC (inflammatory - 45%, goblet-like - 24%, stem-like - 21%, TA - 6%, enterocyte - 3%) and 4 subtypes in EC (inflammatory - 36%, stem-like - 36%, goblet-like - 14%, TA - 14%) were present. Inflammatory MSI tumours from all the three cancer types were significantly ($p < 0.05$) enriched for genes associated with checkpoint inhibition (PDL1), MHC Class I, Type I interferon response and macrophages compared to goblet-like MSI tumours. On the other hand, goblet-like MSI cancer showed enrichment of B-cells.

Conclusions: MSI tumours are heterogeneous and can be stratified by virtue of differentiation states (or cell-of-origin) and different immune phenotypes. With further studies, this heterogeneity may help select MSI cancer patients for immune checkpoint combination therapies.

Legal entity responsible for the study: Anguraj Sadanandam

Funding: NIHR Biomedical Research Centre at the Royal Marsden Hospital and Institute of Cancer Research, London, UK; Cancer Research UK.

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109P Clinical implication of PLR and PD-L1 in breast cancer patients

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Background: Anti-tumor action of the host immune systems and cancer-immune interaction are associated with tumor prognosis. Programmed death ligand-1 (PD-L1) expression was found as an unfavorable prognostic factor in breast cancer in our previous study. Besides, PD-L1 and biomarkers of the host immunity which included Neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR) have been reported in predicting prognosis of biliary tract cancer. However, combination of NLR/PLR and PD-L1 in breast cancer has not been reported. The aim of this study is to evaluate the prognostic role of NLR/PLR and PD-L1 in breast cancer.

Methods: A total of 870 patients with breast cancer treated in Sun Yat-Sen University Cancer Center from 2000 to 2012 with known PD-L1 status were included. Clinicopathological data and pretreatment complete blood count were retrospectively collected. X-tile was used to generate the optimal cut-off value of NLR and PLR. Kaplan-Meier and univariate Cox proportional hazards model analyses were used to compare the survival of patients between different groups.

Results: High PLR group achieved worse result than low PLR group in OS and DFS (5-year OS rate: 82.6% vs 88.8%, $p = 0.010$; 5-year DFS rate: 78.7% vs 85.6%, $p = 0.003$). High PLR was associated with shorter DFS (adjusted HR = 1.540, 95%CI: 1.124-2.110, $p = 0.007$), while high PLR was not an independent factor for OS (adjusted HR = 1.001, 95%CI: 0.999-1.003, $p = 0.488$). NLR was not associated with patients'

survival outcome. And we found patients with PD-L1 expression and high PLR had the worst prognosis. The 5-year DFS rates were 68.4%, and 85.8% in high PLR+PD-L1 (+) group and low PLR+PD-L1 (-) group respectively ($p = 0.002$). The 5-year OS rates were 73.4% and 90.1%, respectively ($p < 0.001$).

Conclusions: High PLR are associated with poor DFS in breast cancer patients. PD-L1 expression combined with high PLR was associated with an aggressive clinical outcome. Further studies are needed to evaluate the predictive value of combination of PD-L1 and peripheral blood immune markers.

Legal entity responsible for the study: Shusen Wang

Funding: National Natural Science Foundation of China (81502302); Science and Technology Program of Guangdong Province (2014A020212384; 2016A020215079)

Disclosure: All authors have declared no conflicts of interest.

110P Prognostic and predictive value of lymphovascular invasion and lymph node status among breast cancer subtypes

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Background: Breast cancer subtype (BCS) and lymphovascular invasion (LVI) have both been independently demonstrated as prognostic factors. The objective of this investigation was to evaluate the prognostic power of LVI and lymph node status among BCSs.

Methods: From an institutional database, 2017 women with a histopathologically confirmed diagnosis of breast cancer treated between January 2006 and December 2014 were consecutively selected for participation in this study.

Results: Of the 2017 patients with breast cancer in the BCS groups, the highest OS and RFS rates were observed in luminal A subtype (93.6% vs. 95.1%, respectively) and the lowest were observed in TN subtype (85.3% vs. 83.0%, respectively). There were significant differences in OS according to the LVI status between the luminal A, luminal B and luminal HER2 subtypes. There were also a significant difference in the RFS rate of the luminal A, luminal B, luminal HER2 and HER2 subgroup. Therefore, we inferred that there were stronger links with LVI and BCS with regard to OS and RFS rates. Kaplan-Meier analysis showed that there were significant differences in the OS and RFS rates according to the LVI status among the BCS groups. There were significant differences in OS according to the LVI status in the distribution of the luminal A, luminal B, luminal HER2, and TN subtypes. There were also significant differences in the RFS rates among the luminal B, luminal HER2, and HER2 subtypes. On multivariate analysis, after controlling for age, tumor size was independently associated with LVI and lymph node status among all BCS groups. There were significant differences in OS according to the status of lymph node-negative and LVI-positive in the luminal HER2 subtype, as well as lymph node-positive and LVI-positive in the TN subtype. There were also significant differences in RFS according to the status of lymph node-negative and LVI-positive in the luminal A subgroup.

Conclusions: LVI and lymph node status were important prognostic factor for OS and RFS among all BCSs. In lymph node-negative breast cancer, luminal HER2 had greater predictive value for OS, whereas luminal A displayed greater predictability for RFS. In lymph node-positive breast cancer, the TN subtype had greater predictive value for OS.

Legal entity responsible for the study: Tri-Services General Hospital, National Defense Medical Center

Funding: None

Disclosure: All authors have declared no conflicts of interest.

111P PD-L1 expression in TNBC: A predictive biomarker of response to neoadjuvant chemotherapy?

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Background: Immune system plays an important role in tumor surveillance and escape. Recently tumor infiltrating lymphocytes (TILs) have been proposed as a predictive biomarker for clinical outcome and pathological response (pR) after neoadjuvant (neoadj) chemotherapy (CT) in breast cancer. PD-L1 is expressed in about 20% of TNBC, suggesting the possibility of being a therapeutic target for this subtype of cancers. Here we studied the association between PD-L1 expression and pR in TNBC.

Methods: We enrolled 54 pts who had received neoadj CT (EC for 4 cycles followed by Paclitaxel q21 for 4 cycles) between Jan 2008 and Dec 2016 at Policlinico Umberto I and San Giovanni Hospital of Rome. We performed IHC for CD20, CD3, CD4, CD8, CD68, N-CAM and PD-L1 (Ventana SP142 clone) in basal paraffin-embedded biopsies. PD-L1 expression on tumor cells was evaluated both qualitatively (membrane staining intensity 0 to 3+) and quantitatively (% of positive cells.). The percentage of TILs positive for PD-L1 was also recorded. Statistical analysis was performed with T di Student test and χ^2 test.

Results: We enrolled 54 pts (median age: 50 y; range 28-75) affected by TNBC: 51 ductal (94.4%), 2 metaplastic (3.7%), 1 lobular (1.9%). The clinical stage before neoadj CT was as follow: 12.9% cT1 (7 pts), 72.2% cT2 (39 pts), 3.7% cT3 (2 pts), 1.85% cT4 (1 pt) and 5.5% cTx (3 pts). 23 pts were cN + (42.5%). After neoadj CT 30 pts underwent mastectomy (55%) and 24 conservative surgery (45%). 19 pts (35%) showed pCR. No significant associations were found between pR and cT, cN, age, histotype and KI-67. In 64.8% of basal biopsies (35 pts) PD-L1 was not detected on tumor cells and in 18.5% (10 pts) it was absent in the immune infiltrate. PD-L1 expression was detected in > 25% of tumor cells in 4 pts, all of which showed pCR ($p = 0.024$). No associations between intensity of membrane staining and pR were detected ($p = 0.7$). The immune infiltrate was characterized mostly by the presence of CD3+ CD8+. No statistically significant associations between and PD-L1 expression on immune infiltrate were detected.

Conclusions: Basal PD-L1 expression on cancer cells was associated with a better pR in TNBC undergoing neoadj CT. The introduction of anti PD-1/PD-L1 therapy in this setting of pts could lead to interesting results.

Legal entity responsible for the study: Sapienza University of Rome

Funding: None

Disclosure: P. Marchetti: Advisory board and meeting with Pfizer, Roche, Novartis, MSD, Bristol-Myers Squibb, Ipsen, AstraZeneca, Boehringer Ingelheim. All other authors have declared no conflicts of interest.

112P Pathological evaluation of tumor infiltrating lymphocytes and the benefit of nivolumab in advanced non-small cell lung cancer (NSCLC)

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Background: Assessment of tumor infiltrating lymphocytes (TIL) by pathologists using Hematoxylin-Eosin (H&E), has been described as a prognostic factor in resected NSCLC. We aimed to correlate TIL to the benefit from nivolumab in patients (pts) with treated advanced NSCLC.

Methods: Patients with advanced NSCLC treated with nivolumab, with biopsy available for evaluation, were included between November 2012 and February 2017 in two cancer centers. Patients characteristics and outcome were collected. The percentage of tumor infiltrating lymphocytes in the stroma was evaluated using H&E staining from archival pretreatment tumor tissue samples. Primary endpoint was to correlate TIL density with progression free survival (PFS).

Results: Out of ninety-eight patients included. 60 (61%) pts were male, with median age of 61 years and 85 (89%) were smokers. Sixty three (73%) pts were PS 0-1. Sixty tumors (61%) were adenocarcinoma, 29 (30%) squamous and 9 (10%) other histologies. Among 83 tumors with known molecular profile, 22 (27%) were KRAS mutated 7 (8%) EGFR mutated, 1(1%) ALK positive. The median treatment line was 3 (2-4). The median follow up was 8 months (m)(95%CI[6-19]). The median PFS was 2 m (95%CI[1-5]). The ORR was for 16%. The median TIL density was 5% (2-15). TIL density $\geq$5% correlated with PFS in univariate and multivariate analysis (HR: 0.48 [0.28-0.82] $p = 0.007$ and HR:0.31 [0.14-0.68] $p = 0.004$ respectively). TIL density $\geq$5% was also associated with better ORR (OR = 3.5, 95%CI [1.06-11.7], $p = 0.04$).

Conclusions: Pathological assessment of TIL allows an easy evaluation of immune infiltration in NSCLC and independently correlates PFS in NSCLC pts treated with nivolumab. Results from validation cohorts and combination with other morphological and immunohistochemical parameters will be reported.

Legal entity responsible for the study: Ithar Gataa

Funding: None

Disclosure: All authors have declared no conflicts of interest.

113P Could a systemic inflammation response index (SIRI) predict overall survival (OS) in metastatic pancreatic cancer (PC)?

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Background: Cancer-associated inflammation is a key molecular feature of PC and may affect the clinical course. The aim of this study was to evaluate the prognostic relevance of SIRI based on peripheral neutrophil, monocyte, and lymphocyte counts in metastatic PC and its association with the metastatic site.

Methods: Retrospective analysis of the medical records of patients with pathologically confirmed metastatic PC between January 2011 and December 2016. Patients were classified as having liver metastases (LM) or extrahepatic metastases alone (EM). Associations with overall survival (OS) were analyzed using Cox proportional models.

Results: A total of 37 patients were included (47 men; median age 63). Median TTP was 4 months and median OS was 6 months. 29 patients (78%) had LM and 8 (22%) EM. 33 patients (89%) received CT: 13 (40%) Gemcitabine (GEM) plus Nab-Paclitaxel, 9 (27%) GEM in monotherapy, 7 (21%) GEM plus Erlotinib and 4 (12%) an Oxaliplatine doublet. Mean Ca 19 9 levels in patients with LM were 199349 and with EM 9107. Univariate analysis identified SIRI scores ≥1,9 as significant risk factor for OS. Age, sex and high CA 19,9 levels had no prognostic significance for OS in all groups. Patients with LM showed a higher SIRI than those with EM (p = 0,03). Patients with SIRI scores < 1,9 (55%) compared to those who had SIRI scores ≥1,9 (45%) had a longer OS (p = 0,01). LM were significantly associated with shorter OS (hazard ratio [HR] 2.79; 95% confidence interval [CI] 1.36-5.34; p = 0,002) but not those with EM (HR 1.83; CI 0.71-4.72; p = 0,2). An SIRI ≥1,9 resulted in a shorter OS compared to an SIRI <1,9 (HR 2.13; CI 1.10–4.10; p = 0.024).

Conclusions: SIRI is associated with survival in patients with metastatic PC. In patients with LM, unfavourable SIRI may be associated with higher tumor burden. In our experience, a baseline SIRI ≥1.9 duplicates the risk of mortality and this finding may allow better risk stratification.

Legal entity responsible for the study: Medical Oncology Department, Hospital Universitario de La Princesa

Funding: None

Disclosure: All authors have declared no conflicts of interest.

114P Molecular imaging with 18F-fluoroestradiol (18F-FES) to assess intra-patient heterogeneity in metastatic breast cancer (MBC): A European TRANSCAN program

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Background: Endocrine responsiveness in Estrogen Receptor positive (ER+) MBC is based on the level of ER expression on the primary tumor and/or metastatic lesion. In this study, nested in the ET-FES JTC 2011 TRANSCAN project, we used molecular imaging with ^{18}F-FES to explore intra-patient heterogeneity in ER expression at different metastatic sites and to identify patients who are not likely to benefit from ET.

Methods: ER+ patients at first relapse underwent at baseline a ^{18}F-FES PET/CT plus a ^{18}F-fluoro-2-deoxy-D-glucose (FDG) PET/CT. Patients were classified into 4 ^{18}F-FES/FDG subgroups based on the proportion of FDG avid metastatic tumor load with high ^{18}F-FES uptake (Gebhart Ann Oncol 2016). Subgroup A was considered positive (100% of concordance); subgroups B and C were considered partially positive or partially negative, with different degrees of ^{18}F-FES uptake; subgroup D was considered negative (100% of discordance). Patients with global SUV ≥2 received first line ET while those with SUV <2 were randomized to ET or to chemotherapy. HR for progression was calculated comparing patients with concordant ^{18}F-FES/FDG lesions (group A) with all the other patients.

Results: So far, 80 patients have been enrolled in the ET-FES trial and 79 are included in the present analysis. At baseline evaluation, 53 patien4ts (67.1%) were classified as ^{18}F-FDG/^{18}F-FES positive (A); 16 patients (20.3%) showed some degree of intra-patient heterogeneity (11 group B and 5 group C); 10 patients (12.6%) were classified as D with all lesions being ^{18}F-FES negative. In the 64 patients with a response evaluation available at time of analysis, 26 have shown progression. ET was administered in 40 patients in group A and in 24 patients in groups B + C + D. The use of ET alone in partially positive (B) or partially negative (C) or negative (D) patients was associated with a 79% absolute increase in the risk of progression (HR 1.79, p 0.2) compared to patients in group A.

Conclusions: Pretreatment ER biomarker imaging at different metastatic sites with ^{18}F-FES PET/CT indicate the presence of a significant intra-patient heterogeneity in MBC and represents a promising tool to select patients who are unlikely to benefit from ET alone.

Clinical trial identification: EUDRACT 2013-000-287-29

Legal entity responsible for the study: E.O. Ospedali Galliera, Genoa, Italy

Funding: TRANSCAN JTC 2011

Disclosure: C. Brambati: Employer Advanced Accelerator Applications. All other authors have declared no conflicts of interest.

115P Evaluation of a predictive radiomics signature for response to immune checkpoint inhibitors (ICIs)

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Background: Radiomics (RAD) uses advanced image processing techniques to extract a large set of quantitative texture and geometric features from tumor regions of interest, and subject these to a supervised machine learning protocol to train a classifier, which we exploit to develop a predictive signature of response to ICIs. We previously developed a lesion-based predictive RAD classifier of response for recurrent/metastatic squamous cell carcinoma of the head and neck (RM SCCHN) pts to ICIs based on RAD features extracted from their CT images (Prawira, ESMO 2016).

Methods: INSPIRE (NCT02644369) is an investigator-initiated phase II study evaluating biomarkers for pembrolizumab (anti-PD1 monoclonal antibody) in multiple cohorts of pts with advanced solid tumors. The primary endpoint of this project is to validate the previously developed RAD classifier from RM SCCHN pts, with pts from INSPIRE. Texture feature algorithm generation and accuracy determination were as previously described. Cross validation accuracy values were generated for combinations of 3 parameters: fraction, cost, and gamma, yielding a 3 dimensional (3D) accuracy space.

Results: Eighty lesions from 23 pts were available for analysis: median age 59, 22% males. Best response: 12 progressive disease, 3 partial response, 8 stable disease (median duration 18 weeks). Primary site: SCCHN/2, triple negative breast cancer/4, high-grade serous ovarian cancer/11, malignant melanoma/2, other advanced cancers/4. Twentyseven lesions were excluded as RECIST 1.1 responses were not yet available. Fiftythree target lesions were contoured. Per lesion RECIST 1.1 radiological outcome: 17 R, 36 NR. Cross validation in the 3D space yielded a set of ROC curves with an accuracy of 71.4% (AUC 0.41, p = 0.7) with 11.2% sensitivity and 99.9% specificity, where specificity corresponds to the proportion of NR tumors classified correctly, and sensitivity to the proportion of R tumors classified correctly.

Conclusions: Heterogeneous histologies and low pt numbers may account for the negative result in this study, suggesting that RAD may be histology-specific. Further validation in a large independent cohort of RM SCCHN pts treated with pembrolizumab is planned.

Clinical trial identification: INSPIRE (NCT02644369)

Legal entity responsible for the study: Princess Margaret Cancer Centre, Drug Development Program

Funding: Merck

Disclosure: All authors have declared no conflicts of interest.

116P Clinical and pre-clinical biomarkers of Regorafenib (REG) efficacy in metastatic colorectal cancer (mCRC) in a phase II trial

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Background: REG demonstrated efficacy in pre-treated mCRC pts. Lack of predictive biomarkers, potential toxicities and cost/effectiveness concerns highlight the unmet need for better patient selection.

Methods: *RAS* mutant mCRC pts with biopsiable metastatic deposits were enrolled in this phase II trial. Tissue biopsies (6-12 cores) were obtained at baseline (BL), after 2 months if stable disease (SD) and at disease progression (PD). Dynamic contrast enhanced (DCE) MRI was acquired pre and at day 15 post-treatment. Median values of volume transfer constant (K^{trans}), enhancing fraction (EF) and their product, KEF [K^{trans}*EF/100] were generated. Circulating tumour (ct) DNA was collected monthly until PD and tested for clonal *RAS* mutations by digital droplet PCR. PDOs derived from responders and non-responders pts were implanted orthotopically in the liver of mice and treated with REG for 5 days. Changes in tumour and fractional blood volume (fBV) were monitored by oxygen-enhanced MRI.

Results: mCRC pts (n = 27) with paired MRI scans were analysed; a single target lesion per pt was chosen (25 liver and 2 pelvic metastases). Median KEF decrease was 58.2%. In the 23 analysable pts (4 received ≤1 cycle of treatment due to toxicities),>70% drop in KEF(8/27) was associated with higher disease control rate (DCR) measured by

RECIST 1.1 at 2 months (m) ($p = 0.05$), progression free survival (PFS) [HR = 0.24 (0.07-0.86), $p = 0.03$], 6-m PFS (43.8% VS 0%) and overall survival (OS) [HR 0.08 (0.01-0.63), $p = 0.02$]. In all pts with DCR, PFS was found to be 5.6 vs. 4.2 m [HR 0.30 (95% CI 0.06-1.49), $p = 0.140$) and OS was 15.2 vs. 5.8 m [HR 0.11 (95% CI 0.01-1.06), $p = 0.057$]. KEF drop correlated with CD-31 reduction in sequential tissue biopsies ($p = 0.04$). RAS mutant clones decay in ctDNA after 8 weeks of treatment was associated with better PFS [HR 0.21 (0.06 - 0.71), $p = 0.01$] and OS [HR 0.28 (0.07 - 1.04), $p = 0.06$]. PDOs xeno-transplants treated with REG compared to controls had significant lower tumour fBV (4.5 VS 10.6, $p = 0.03$) and lower microvascular density measured by CD31 staining (4.3 VS 8.9, $p = 0.02$).

Conclusions: Combining DCE-MRI and ctDNA predicts depth and duration of anti-angiogenic response to REG with potential health economic implications.

Clinical trial identification: clinical trials.gov number NCT03010722

Legal entity responsible for the study: The Royal Marsden NHS Foundation Trust

Funding: Bayer Oncology Group

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117P Anti-HER2 therapy efficacy in HER2-negative metastatic breast cancer with HER2-amplified circulating tumor cells: results of the CirCe T-DM1 trial

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Background: Changes of HER2 status has been reported in circulating tumor cells (CTC) isolated from preclinical models and metastatic breast cancer (MBC) patients. The prospective multicentric phase II "CirCe T-DM1" trial was set up to assess whether HER2-amplified CTC are detectable in HER2-negative MBC and whether these cancers would respond to anti-HER2 therapy.

Methods: HER2-amplified CTC were screened in HER2-negative (HER2-/ER- and HER2-/ER+) MBC patients starting a 3rd line or 4th line of systemic therapy. CTC were detected by CellSearch® (Janssen Diagnostics) and FISH was performed on isolated CTCs. HER2-amplification was defined by a HER2/CEP17 ratio $\geq$2.2. Patients with $\geq$1 HER2-amplified CTC, measurable disease and adequate organ function were eligible. After stratification according to amplified CTC count ($<$ vs $\geq$ 3), patients received single agent T-DM1. The primary endpoint of the study was the response rate by RECIST criteria.

Results: From 11/2013 to 08/2016, 155 MBC patients were screened. 11 (9.2%) and 3 patients (2.5%) had 1-2 and $\geq$3 HER2-amplified CTCs respectively (minimal HER2/CEP17 ratio: 2.5). In the 14 patients with HER2-amplified CTC, the fraction of HER2-amplified CTCs among all detected CTCs was low (median 1.6%, range [0.3%-35.3%]), and presence of HER2-amplified CTCs was not associated with any patients' characteristics. 11 patients were treated with single agent T-DM1. Partial response was confirmed in one patient with 1 HER2-amplified CTC (among 9 CTC detected); median PFS was 4.9 months (range: 1.8-10.1).

Conclusions: This study shows that CTCs with a true HER2-amplification can be detected in advanced HER2-negative MBC, mostly as a minor CTCs subset. Although one confirmed response was observed in our study, the overall low response rate to specific anti-HER2 therapy does not support the clinical utility of such strategy in that setting.

Clinical trial identification: NCT01975142

Legal entity responsible for the study: Institut Curie

Funding: Roche

Disclosure: All authors have declared no conflicts of interest.

118P Nationwide external quality assessment (EQA) of EGFR testing in circulating tumor DNA: The French experience

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Background: Detection of EGFR mutation in circulating tumor DNA (ctDNA), a powerful blood-based biomarker with multiple clinical applications for lung cancer patient, is technically challenging because it requires sensitivity and specificity. In order to evaluate the performance of the french laboratories performing this assay, we set up a national EQA scheme for circulating tumor DNA.

Methods: Artificial samples were prepared by spiking DNA extracted from control FFPE sections containing specific mutations (Horizon Diagnostics, from 25 to 350 copies/mL of plasma, as determined by digital PCR) in normal plasma (Clinisciences). Aliquots (2 ml) of 10 different samples were sent in dry ice to 43 laboratories. DNA extraction and EGFR testing were performed according to local practice. Laboratories were requested to search for exon 19 deletions, p.L858R, p.G719X and p.T790M mutations. Data were collected on a web questionnaire within one month and compared to the expected results.

Results: We collected 30 complete sets of data. DNA was extracted using the QIAmp® circulating DNA kit (Qiagen; n = 13), the Cobas® cfDNA sample preparation kit (Roche; n = 9) or the Maxwell® system (Promega; n = 7). The most widely used methods were the Cobas® EGFR Mutation Test v2 (Roche; n = 10), digital PCR (n = 8) and NGS (n = 6). Among the 10 labs using the Cobas®, 9 obtained the 10 expected genotypes. This number dropped to 3 (out of 6 labs) for NGS, and 2 (out of 8 labs) for dPCR, because of false negative results, false positive results, and not contributive tests.

Conclusions: Digital PCR and NGS are known to be highly sensitive techniques. However, the results of this EQA suggest that in routine clinical practice, ctDNA analysis requires technical skill or/and validated bioinformatic pipeline to reach high sensitivy and specificity. Under the specific conditions of this scheme, the Cobas® method appeared to be the most robust approach. This external control will allow the laboratories to evaluate their practice and improve their process. A similar approach targeting other genes (BRAF, KRAS and NRAS) is being developed, and additional EQA schemes will be set up at the nationwide level. Supported by a grant from AstraZeneca.

Legal entity responsible for the study: Gen&Tiss

Funding: AstraZeneca

Disclosure: All authors have declared no conflicts of interest.

119P IL-8 as a pharmacodynamic biomarker for TGF-β2 antisense (trabedersen) therapy: Results of a phase II trial

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Background: In a Phase I/II study of Trabedersen (OT-101), a phosphorothioate antisense specific for human TGF- β2 mRNA, patients with advanced pancreatic cancer (PAC) treated in the 2nd-line and beyond exhibited improved overall survival (OS) when OT-101 was followed with chemotherapy. Here, we examined the association between plasma levels of cyto-/chemokines and OS outcomes to identify potential biomarkers for improved OS.

Methods: 37 PAC patients were treated with continuous IV infusion in escalating doses of 2 treatment schedules (7-days-on, 7-days-off and 4-days-on, 10-days-off). Plasma levels of 31 cyto-/chemokines were measured at 8 separate time points over 3 cycles of OT-101 treatment (140 mg/m^2/day, 4-days-on, 10-days-off). Standardized maximum levels of individual cyto-/chemokines on Day 2 were subtracted from levels on Day 5 of each cycle of treatment and correlated with log10 transformed OS values. Feedback interactions with PK parameters were also investigated utilizing an ANCOVA model.

Results: A median OS of 14.5 months and 2.6 months was observed for 2nd-line patients treated with and without subsequent chemotherapies, respectively ($p = 0.0009$). Increasing difference of IL-8 levels at Day 2 vs Day 5 was positively correlated with OS ($R^2 = 0.58$, $P = 0.0066$). Stratifying for patients with and without chemo, R^2 increased to 0.99 and 0.77 respectively. Similar results were observed for IL-15, with $R^2 = 0.93$ in patients with chemo and $R^2 = 0.50$ in those without. ANCOVA models for two PK parameters exhibited significant model fits ($F_{3,7} = 7.89$, $P = 0.012$ for Simulated Vz Mean; $F_{3,7} = 8.18$, $P = 0.011$ for Simulated Cl Mean) and the interaction effects resulted in lower p-values for the correlation of OS vs IL-8 levels.

Conclusions: Increasing peak levels of IL-8 and IL-15 response on Day 2 of OT-101 treatment correlated with OS in PAC patients. This correlation with OS was evident regardless of subsequent chemotherapy or not indicating spikes in IL-8 and IL-15 as potential biomarkers for OT-101.

Legal entity responsible for the study: Oncotelic Inc.

Funding: Oncotelic Inc.

Disclosure: L. Hwang, W. Wang, S. Qazi, K. Ng, O. D'cruz, V. Trieu: Employee

120P Predictive assay for anti-angiogenic agents (AADx) identifies molecular subgroups of RASwt mCRC with differential efficacy of FOLFIRI plus bevacizumab in the FIRE-3 (AIO KRK-0306) trial

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Background: The FIRE-3 trial compared 1st-line therapy of FOLFIRI plus either cetuximab or bevacizumab in 592 KRAS exon 2 wildtype (wt) mCRC patients. The subgroup of extended RAS wt patients consisted of 400 patients. The AADx molecular assay has previously been shown to identify a poor prognosis angiogeneic subgroup across multiple cancer types including colorectal cancer. Both bevacizumab (through inhibition of VEGFR-activation) and cetuximab (through inhibition of EGFR-signaling) would be expected to have anti-angiogenic effects in colorectal cancer. The predictive role of AADx in FOLFIRI plus bevacizumab or cetuximab treated in colorectal cancer patients remains unclear.

Methods: Transcriptional profiling of 501 formalin fixed paraffin embedded pre-treatment samples from the ITT population was performed using the Almac Diagnostics Xcel™ array. Patients were classified by the AADx assay as ANGIO ON or OFF based on a predefined score. ORRs were compared using Fischer's exact test. Progression free survival (PFS) and Overall survival (OS) times were compared using Kaplan-Meier estimation and log-rank tests. Hazard ratios (HR) were estimated according to the Cox proportional hazard method.

Results: The AADX assay was successfully applied to 438 out of 501 specimens available from the study population (n = 752). Of those, 315 had a RAS wt tumor and 123 a RAS mutant. The correlation between RAS status and AADx score with respect to ORR; PFS, and OS were complex (Table). The addition of cetuximab to FOLFIRI was significantly superior to the addition bevacizumab in "ANGIO ON" tumors most likely reflecting the strong link between EGFR-signaling and angiogenesis in colorectal cancer.

Conclusions: Here, we present data demonstrating that it possible to define subgroups in the group of wt mCRC patients within the FIRE-3 trial that responded differently to the addition of cetuximab or bevacizumab.

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Legal entity responsible for the study: Klinikum der Universität München

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121P Influence of HIF-2alpha deregulation and overexpression of VEGF ligands on the response to aflibercept: Identification of predictive biomarkers

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Background: Angiogenesis inhibitors are widely used for treatment of metastastic colorectal cancer. However, no predictive biomarkers are currently available for patient selection. Besides the tumor-associated endothelial cells, VEGF-signaling inhibitors target CRC cells that express VEGF as well as functional VEGFR1 receptors thereby mediating both paracrine and autocrine VEGF-signaling. The aims of this work is i) to establish the direct influence of aflibercept (Zaltrap®) that inhibits all three VEGFR1 ligands (VEGF-A, VEGF-B and PlGF) on CRC cells, ii) to identify tumor phenotypes associated with resistance to aflibercept in vitro and, iii) to extend these findings to human xenograft models.

Methods: A panel of 12 well-characterized CRC cell lines was used to establish the influence of VEGFR1 stimulation (VEGF-A, VEGF-B, PlGF) and inhibition (aflibercept) on VEGF-mediated tumor cell migration. Expression of VEGF ligands and receptors was determined by qRT-PCR and ELISA assays. The *in vivo* influence of aflibercept was determined in human xenograft models and complemented by IHC and Western blot analysis.

Results: Aflibercept inhibited the migration of most CRC cells under both normoxia and hypoxia including the highly sensitive HCT-116 cells. In contrast, LS174T cells did not respond to either aflibercept or to purified VEGF ligands. These cells expressed high levels of VEGF ligands and HIF2alpha, even under normoxia. Accordingly, aflibercept showed pronounced *in vivo* activity toward HCT-116 xenografts with 75% tumor growth inhibition but only 40% tumor growth inhibition toward LS174T tumors, compared to the corresponding vehicle controls. A similar trend was observed for bevacizumab with 41% tumor growth inhibition for HCT-116 and 32% inhibition for LS174T xenografts. IHC analysis of LS174T xenografts confirmed the strong expression of HIF2alpha and VEGF ligands as well as a modest inhibitory effect on the tumor-associated endothelia cells.

Conclusions: We here report that aflibercept has direct antimigratory effects on most CRC cells. Strong expression of HIF-2alpha and VEGF ligands was accompanied by aflibercept resistance in vitro as in vivo.

Legal entity responsible for the study: INSERM U938 and Université Pierre et Marie Curie (UPMC), Sorbonne Universités, Paris, France

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122P Cell-free (cf)DNA analysis identifies *PIK3CA/AKT1* mutations associated with greater PFS improvement from the addition of ipatasertib (IPAT) to paclitaxel (P) in triple-negative breast cancer (TNBC)

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Background: The oral Akt inhibitor IPAT is being evaluated in cancers with a high prevalence of PI3K/Akt pathway activation. In the placebo-controlled randomised phase II LOTUS trial (NCT02162719), adding IPAT to P as first-line therapy for metastatic TNBC improved PFS in unselected patients (stratified hazard ratio [HR] 0.60 [90% CI 0.40–0.91]), with a more pronounced effect in patients with *PIK3CA/AKT1/PTEN*-altered tumours [Dent, ASCO 2017]. cfDNA sequencing was performed to assess the utility of blood samples for detecting tumour mutations in TNBC.

Methods: Pre-treatment plasma and tumour samples were evaluated for genetic alterations using Foundation Medicine's FoundationACT® and FoundationOne® next-generation sequencing assays, respectively. Samples from 88 patients were evaluable by cfDNA, 72 of whom also had evaluable tumour samples (52 primary tumour).

Table: 120P

RAS wild-type	AADx score	ORR	p OR	PFS months	p HR	OS months	p HR
FOLFIRI + Cetuximab	ANGIO ON	65.2%	0.69 0.87	10.6	0.72 1.07	29.8	0.88 1.04
	ANGIO OFF	68.3%		10.6		30.6	
FOLFIRI + Bevacizumab	ANGIO ON	46.3%	0.0038 0.39	9.1	0.0002 0.52	21.2	0.0062 0.59
	ANGIO OFF	69.1%		13.1		29.1	
RAS Mutant	**AADx score**	**ORR**	**p OR**	**PFS months**	**p HR**	**OS months**	**p HR**
FOLFIRI + Cetuximab	ANGIO ON	38.6%	0.93 0.94	8.2	0.49 1.23	23.0	0.81 0.92
	ANGIO OFF	40.0%		7.7		19.2	
FOLFIRI + Bevacizumab	ANGIO ON	58.8%	0.13 2.1	11.2	0.35 1.30	23.1	0.02 2.00
	ANGIO OFF	40.0%		10.2		18.5	

To test the prognostic effect of cfDNA mutational burden, patients were classified as having high or low variant allele fraction (VAF) in cfDNA using the median as a cutoff.

Results: In 81 patients (92%), at least one mutation was detectable by cfDNA sequencing. Concordance with tissue sequencing was 75%. High VAF was associated with shorter PFS than low VAF in both the IPAT + P arm (HR 2.39 [90% CI 1.19–4.70]) and the placebo + P arm (HR 2.68 [90% CI 1.46–5.11]). High VAF was also associated with the presence of > 1 metastatic site but not tumour volume per RECIST v1.1. In 22 patients (25%), an activating PIK3CA (n = 16) or AKT1 (n = 6) mutation was detected in cfDNA; concordance with tissue sequencing was 100%. PFS improvement with the addition of IPAT to P was more pronounced in patients with detectable PIK3CA/AKT1 mutations (HR 0.15 [90% CI 0.03–0.50]) than in those without a detectable mutation (HR 0.82 [90% CI 0.50–1.31]).

Conclusions: These results highlight the potential role of cfDNA in evaluating patient prognosis as well as identifying genetic markers associated with improved treatment outcomes. Furthermore, they support the occurrence of PIK3CA and AKT1 mutations as early genetic events present in primary tissue samples that are maintained during metastasis.

Clinical trial identification: NCT02162719

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

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Disclosure: M. Wongchenko: Employee of Genentech, Inc. and holds shares in Roche and Ariad Pharmaceuticals. R. Dent: Honoraria for consultancy/advisory boards/speaker engagements from Pfizer, Roche, Eisai, Merck, and AstraZeneca. S-B. Kim: Research funding from Novartis, Sanofi-Aventis, Kyowa-Kirin Inc, and Dongkook Pharma Co., Ltd. C. Saura: Honoraria for consulting/advisory roles from Puma Biotechnology, Pfizer, and Roche and research funding (to her institution) from Genentech and AstraZeneca. M. Oliveira: Honoraria for consulting/advisory roles from Puma Biotechnology and Genentech/Roche and research funding (to the institution) from Genentech and AstraZeneca. J. Baselga: Compensation for a leadership role from Infinity Pharmaceuticals, stock or ownership interest in PMV Pharma, Juno Therapeutics, Infinity Pharmaceuticals, and GRAIL, and honoraria for consulting/advisory role for Eli Lilly, Novartis, and GRAIL. A.V. Kapp, W.Y. Chan, S.M. Singel, D.J. Maslyar, S. Gendreau: Employee of Genentech, Inc. and holds stock in Roche.

123P Genotyping circulating tumor DNA identifies metastatic colorectal cancer (mCRC) patients highly sensitive to Sym004

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Background: Acquired resistance of mCRC patients (pts) to anti-EGFR monoclonal antibodies (mAbs) is frequently due to mutations in RAS/BRAF and EGFR extracellular domain (ECD), and amplifications in MET/ERBB2. Studies suggest that some anti-EGFR mAb refractory pts retain tumor EGFR-dependency potentially targetable by more efficacious agents such as Sym004 – a mixture of two non-overlapping mAb targeting EGFR for degradation. A Phase 2b trial of Sym004 in 254 mCRC pts tissue RAS wt that relapsed on anti-EGFR blockade was recently completed.

Methods: Baseline circulating tumor (ct)DNA profiles (Guardant360, Guardant Health, N = 193 pts) were obtained from blood samples collected from pts in the Sym004 Phase2b trial. Serial blood samples during treatment were analyzed for EGFR-ECD mutation dynamics.

Results: High mutant allele frequency (MAF >20%) of *KRAS*/*NRAS* was found in 5% of pts and *BRAF* V600E and *EGFR*-ECD mutations in 6.7% and 25% of pts, respectively. At least 1 of these mechanisms of resistance was identified in 32% of the pts. Mutations in *KRAS, NRAS*, and *BRAF* V600E, and amplifications of *ERBB2* and *MET* were more likely to co-occur with *EGFR*-ECD mutations, demonstrating genomic complexity developed as a result of EGFR blockade. Comparative analysis of MAFs of driver genes indicated that *EGFR*-ECD mutations are subclonal events. The absence of any *EGFR*-ECD/*BRAF*/high *RAS* MAF mutation at baseline was associated with a significantly improved OS in the Sym004 treated pts as compared to control arm with investigator's choice chemotherapy. Sym004 has previously been demonstrated to retain *in vitro* efficacy in *EGFR*-ECD mutated cancer cells, and ctDNA monitoring demonstrated decrease in *EGFR*-ECD in Sym004 treated pts. This suggests that *EGFR*-ECD mutated cells are targeted by Sym004, but this activity does not translate into clinically meaningful OS benefit, likely due to other co-occuring resistance mechanisms.

Conclusions: Comprehensive liquid biomarker profiling of 193 mCRC pts captured high intrapatient heterogeneity following anti-EGFR therapy, and identified a highly Sym004 sensitive mCRC pts subset with a *RAS/RAF/EGFR*-ECD wild type profile. Our data indicates heterogeneous responses of different subclones to targeted agents in mCRC.

Legal entity responsible for the study: Medical Oncology Department, Hospital del Mar, Barcelona, Spain

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Disclosure: C. Montagut Viladot: Advisory Board for Amgen, Bayer, Merck Serono, Sanofi, Symphogen. T. Tuxen Poulsen, M. Kragh, K. Koefoed, C. Ding, J. Clausell-Tormos, T. Lindsted, M.W. Pedersen, P. Nadler, I.D. Horak: Full time employee at Symphogen. S. Kopetz: Advisory boards for Amgen, Merrimack, Bayer, Sanofi, Array BioPharma, Genentech, MolecularMatch, Symphogen, Guardant Health, EMD Serono, Merck. J. Tabernero: Advisory boards for Amgen, Bayer, Boehringer Ingelheim, Celgene, Chugai, Genentech, Lilly, MSD, Merck Serono, Novartis, Pfizer, Roche, Sanofi, Symphogen, Taiho, and Takeda. All other authors have declared no conflicts of interest.

124P Role of circulating miRNAs as prognostic biomarkers in resected early-stage non-small cell lung cancer

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Background: Non-small cell lung cancer (NSCLC) is the primary cause of cancer-related death, with a 5-year survival rate < 16% mainly because of disseminated disease, even in fully resected early-stage disease. Biomarkers identifying patients at a higher risk of relapse would be useful and circulating microRNAs (miRNAs) are a promising option in this setting.

Methods: We analyzed a case series of 182 patients with resected early stage (IA-IIIA) NSCLC (99 adenocarcinoma [ADC] and 83 squamous cell carcinoma [SCC]). Peripheral blood samples were collected from each patient before surgical resection and serum was obtained after centrifugation and stored at -80 °C until miRNA extraction. A panel of 84 circulating miRNAs was analyzed by Real Time PCR. Data were normalized using an external spike-in (cel-miR-39) and the mean of the two most stable endogenous housekeeping genes chosen separately for ADC and SCC samples. miRNA expression was analyzed in relation to disease-free survival (DFS) by the Cox regression model. Results are reported as hazard ratios (HRs) and 95% confidence intervals (CIs).

Results: In ADC patients, stage was significantly associated with DFS (HR stage II-IIIA *vs* stage I = 4.94, 95% CI [2.71 - 9.02]). Multiple statistical methods were used to evaluate miRNA expression data. In univariate analysis, two miRNAs (miR-222-3p and miR-22-3p) were significantly associated with DFS (p = 0.033 and p = 0.041, respectively). However, this significance was not maintained after adjusting for multiple testing. In SCC patients, disease stage was significantly related to DFS (HR stage II-IIIA *vs* stage I = 3.31, 95% CI [1.74 - 6.33]). Five miRNAs (let-7a-5p, miR-126-3p, miR-26a-5p, miR-130b-3p, miR-21-5p) were significantly associated with DFS even after adjusting for multiple testing (False Discovery Rate q-value <0.001).

Conclusions: Pre-surgery circulating levels of let-7a-5p, miR-126-3p, miR-26a-5p, miR-130b-3p and miR-21-5p would appear to be significantly correlated with prognosis in resected early-stage SCC.

Legal entity responsible for the study: IRST-IRCCS

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Disclosure: All authors have declared no conflicts of interest.

125P Targeted methylation sequencing of plasma cell-free DNA identifies patients with advanced breast, colorectal, non-small cell lung cancer, melanoma with poor outcomes

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Background: Plasma cell-free DNA (cfDNA) sampling from patients with advanced cancers offers a minimally invasive source of tumor DNA for molecular testing, including methylation profiling. Tumor sequencing at disease progression offers insights into cancer biology, but is often not done because of logistical and other challenges associated with tumor biopsies.

Methods: Plasma samples were collected from patients with advanced breast, colorectal, non-small cell lung cancer (NSCLC) and melanoma at the time of disease

progression and/or on therapy. Up to 30 ng (median 18ng) of plasma cfDNA was tested with the pan-cancer methylation panel to target a total of 10,888 CpG sites using an Illumina HiSeq2500 sequencer to calculate methylation scores. Methylation scores were correlated with cancer types and clinical outcomes.

Results: Of 69 plasma cfDNA samples collected from patients (colorectal cancer, 28; NSCLC, 18, breast cancer, 12; melanoma, 11) at disease progression, methylation scores were consistent with the presence of cancer in 84% (58/69); while in 79% (46/58) of plasma cfDNA samples, methylation scores accurately classified the underlying cancer type. High methylation scores in plasma cfDNA samples collected at disease progression compared to low methylation scores were associated with shorter survival irrespective of the tumor type (3.9 vs 10.4 months, $P < 0.001$, confirmed on multivariable analysis). In addition, high methylation scores in plasma cfDNA samples collected at progression vs low methylation scores were associated with shorter time to treatment failure (TTF) on systemic therapy (1.6 vs. 2.8 months, $P = 0.007$). There was a positive correlation between RECIST response (%) to systemic therapy and methylation scores (r 0.32, $P = 0.03$). Methylations score before therapy (median 87.28) were higher than methylation scores on therapy (median 9.49, $P = 0.001$).

Conclusions: Methylation scores from plasma cfDNA collected at disease progression from patients with advanced cancers accurately classify underlying cancer types and are associated with survival, TTF and RECIST responses.

Clinical trial identification: MD Anderson Protocols laboratory protocols LAB10-0334 and PA13-0956

Legal entity responsible for the study: MD Anderson Cancer Center

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126P Single-cell combined mutation and gene expression studies of circulating tumor-associated cells in non-small cell lung cancer

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Background: Circulating tumor cells (CTC) in the bloodstream not only provide us a sampling of the tumor population but are also keys to the metastatic process. Most CTC enrichment devices are coupled to downstream marker analysis by immunocytochemistry that define CTC as CD45-negative and epithelial marker (e.g. EPCAM)-positive cells. Our group recently reported a new class of tumor-derived cells in circulation, the circulating tumor-endothelial cluster, in colorectal cancer. This demonstrated that tumor-associated cells in circulation hitherto considered malignant may instead and unexpectedly provide key insights to the tumor microenvironment. To effectively classify the circulating cell milieu in lung cancer, we used a single-cell technique RNA and mutation analysis (scrm-PCR) we have described previously to characterize DNA and RNA from the same cell.

Methods: We enriched for CTC from whole blood of non-small cell lung cancer (NSCLC) patients using silicon microsieves with uniformly spaced 8 to 10uM circular pores. We manually selected captured single cells or cell clusters for characterization. 50 single cell or cell clusters from 5 NSCLC patients and 2 healthy subjects were probed for a curated panel of 27 RNA markers and hotspot DNA mutations in EGFR, TP53 and KRAS by scrm-PCR.

Results: Classic epithelial markers such as EPCAM are largely unexpressed in CD45-negative cells in NSCLC. DNA mutations were undetected in all isolated cells except for 1 cell. CD45-negative cell clusters in NSCLC exhibit a different phenotypic profile as compared to our report of tumor-endothelial in colorectal cancer, failing to express classic endothelial markers such as VWF, MCAM and CDH5. We identified important morphological features correlating with biological phenotypic classification of these cells, allowing us to establish a map of the circulating cell milieu of NSCLC.

Conclusions: This is the first systematic same-cell combined mutation and expression analysis of circulating cells in NSCLC patients. With this novel approach, we report the presence of predominantly tumor-associated cells rather than malignant cells in circulation, and highlight the potential of these cells as biomarkers of NSCLC and its tumor microenvironment.

Legal entity responsible for the study: Institute of Bioengineering and Nanotechnology

Funding: Agency for Science, Technology and Research (A*STAR)

Disclosure: All authors have declared no conflicts of interest.

127P EGFR copy number aberrations detected in cfDNA from advanced NSCLC patients

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Background: Copy number aberrations (CNA) in the epidermal growth factor receptor (EGFR) represent a mechanism of tyrosine kinase activation and oncogenic signaling in advanced non-small cell lung cancers (NSCLC). High copy number gains (CNG) may predict TKI sensitivity but when acquired are postulated to reflect resistance. Treatment with monoclonal antibodies may have a role and therefore CNA integration in molecular diagnostics is potentially important.

Methods: Cell free (cf) DNA was from extracted from NSCLC patients undergoing treatment with EFGR-TKIs. A validated Liquid Biopsy Sequencing (LB-Seq) method for hybrid capture followed by ultra deep sequencing (> 20,000X) evaluated coding exons of KRAS, NRAS, BRAF, PIK3CA, and EGFR (18 kb). Subsequent filtering of mutation calls using a novel algorithm enabled detection of tumor-derived fragments at concentrations down to 0.2%. EGFR CNAs were assessed using a modified version of the VisCap algorithm. Mutation calls were compared to tissue biospy results for EGFR mutations.

Results: Targeted sequencing has been performed on 12 samples to date: 10 patients with classical *EGFR* mutations in L858R and del19, 1 with an exon 20 insertion and 1 with an exon 18 G718X mutation. All patients had progressed on at least one *EGFR*-TKI. % mutant reads ranged from 0.25% to 33%. *EGFR* CNGs were detected in 3 patients: 1 patient with T790M+ve disease confirmed in both tissue and cfDNA was found to have a co-occurring BRAF mutation (p.33_34insGA). The remaining 2 patients' tissue samples tested negative for T790M; T790M was detected in cfDNA in 1 patient, who is currently receiving osimertinib, and in the other patient rapid progression on gefitinib occurred with an *EGFR*-G719X mutation. Copy number losses were detected in 2 patients. 2 of 6 patients with *EGFR*-T790M positive tissue were confirmed in cfDNA, the remaining 4 negative results were verified by ddPCR. An intronic variant of unknown significance (c.747 + 9C>T), not covered in tissue testing, was also captured in cfDNA.

Conclusions: Copy number aberrations in EGFR can be detected from targeted sequencing of cfDNA in patients with *EGFR* mutated NSCLC. Longitudinal evaluation in patients receiving *EGFR*-TKIs may provide insights into mechanisms of resistance.

Legal entity responsible for the study: Natasha Leighl

Funding: None

Disclosure: N.B. Leighl: Research funding (institution): Novartis. Travel/honoraria: AstraZeneca, Merck Sharp Dohme, Pfizer, Bristol-Myers Squibb. All other authors have declared no conflicts of interest.

128P Detection of esophageal cancer patients using circulating serum microRNA from the result of comprehensive analysis

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Background: Recent studies have reported that serum microRNAs (miRNAs) are potentially useful biomarkers for diagnosis and treatment of cancer. However, its utility for detecting esophageal squamous cell carcinoma (ESCC) has not been investigated yet. The aims of this study are to identify circulating serum miRNAs for ESCC detection.

Methods: We comprehensively analyzed serum miRNA expression profiles of 595 patients with ESCC, and 5051 non-cancer individuals using microarray (3D-Gene, Toray). Serum of non-cancer individuals was obtained from Biobank of NCGG and Health check up clinic (Yokohama Minoru clinic). Serum of ESCC patients was collected before starting any treatment such as radiotherapy, surgery and chemotherapy. Analyzed samples were randomly divided into discovery and validation sets. Serum miRNA levels were compared between ESCC and non-ESCC patients. Fisher's linear discriminant analysis was performed to construct the discriminant model for ESCC detection. Measured values of each miRNAs were extrapolated into the discriminant formulas. We performed ROC analysis to evaluate the diagnostic ability of these formulas in each validation cohort.

Results: In discovery set, 300 patients of ESCC was compared to 300 individuals of non-cancer control. We picked up 3 miRNAs, named miR-A, miR-B and miR-C, for ESCC diagnosis. Their AUC for detection of ESCC was 0.967, 0.873 and 0.650, respectively in ROC analysis. We constructed the discriminant model, called EC index, using these 3 miRNAs in discovery set. In validation set which contain 295 pts of ESCC and 4751 person of non-cancer control, EC index showed the AUC, sensitivity and specificity of the discriminant formula was 0.99, 0.98 and 0.95, respectively.

Conclusions: We identified novel serum miRNAs for ESCC detection. Our discriminant using these miRNAs can diagnose ESCC.

Clinical trial identification: NCCH2016-249

Legal entity responsible for the study: National Cancer Center

Funding: Japan Agency for Medical Research and Development

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129P First prospective multicenter real-world RAS mutation comparison between OncoBEAM-based liquid biopsy and tissue analysis

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Background: Liquid biopsy is a powerful tool to refine the management of cancer patients by offering a minimally-invasive alternative to tumor tissue testing and rapid evaluation of overall tumor burden mutational status. To support its clinical adoption, a rigorous real-world evaluation of this method in routine clinical practice is required. OncoBEAM RAS is the only liquid biopsy assay to attain CE-IVD status for plasma RAS mutation analysis in routine colorectal cancer (CRC) patient care. The goal of the present study was to evaluate the aggregate performance of OncoBEAM RAS in10 hospital labs where the technology is installed in Spain.

Methods: Blood samples were collected in Streck cell-free DNA BCT® or EDTA tubes from metastatic CRC patients and circulating cell-free DNA from plasma was examined for RAS mutations using the OncoBEAM platform at each hospital laboratory. Results were then compared to those obtained from DNA extracted from tissue from the same patient.

Results: The overall percentage agreement (concordance) of results from plasma and tissue RAS mutation testing of 230 patients was 90.4% (208/230); 95% CI = 0.86-0.94, with positive percent agreement of 86.9% (113/130) and negative percent agreement of 95.0% (95/100). Re-analysis of tissue from all discordant cases by BEAMing revealed 2 false negative local tumor tissue RAS results. Plasma false negative results were observed more frequently in patients presenting with peritoneal and/or lung metastases only. The prevalence of RAS mutations in plasma (51.3%) and tissue (56.5%) were in accord with the expected occurrence of RAS mutations in mCRC patients.

Conclusions: In this first prospective real-world RAS mutation performance comparison study across a network of hospital laboratories certified to perform OncoBEAM testing in routine clinical practice, a high overall agreement was observed between results obtained from plasma and tissue samples. These results are comparable to those obtained in retrospective studies. Overall, these findings indicate that plasma OncoBEAM RAS testing is a viable solution for rapid delivery of RAS mutation status to determine mCRC patient eligibility for anti-EGFR therapy.

Legal entity responsible for the study: University Hospital "Fundacion Jimenez Diaz", Autonomous University of Madrid

Funding: Sysmex, Merck

Disclosure: All authors have declared no conflicts of interest.

130P EGFR plasma testing in routine practice by real-time PCR in lung cancer patients: Experience of 262 patients

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Background: EGFR mutation testing in lung cancer prior to tyrosine kinase inhibitor (TKI) therapy can be performed in tissue or plasma in practice. Both techniques are complementary; however, plasma testing can represent a surrogate for re-sampling a tumour in patients progressing under TKI prior to prescription of osimertinib, but clinical sensitivity of the test remains to be determined. We present our twelve-month experience of integrating EGFR plasma testing into our service with a series of 262 cases. We currently receive over 50 cases per month.

Methods: EGFR mutation testing for both tissue and plasma is performed using cobas EGFR Mutation Test v2, which covers 29 deletions in exon 19, T790M, L858R, G719X, S768I, L861Q and 5 insertions in exon 20. For plasma testing, DNA is extracted using the cobas cfDNA sample preparation kit. All samples were submitted in Paxgene ccfDNA tubes.

Results: Of the 262 cases submitted for testing, five failed (1.9%). 123 mutations, including 42 T790M, were detected. Turnaround time was two days. Clinical sensitivity is very difficult to assess because of the uncertainty of the presence of circulating tumour DNA at all. All types of primary mutation were detected: 70 exon 19 deletions, 42 L858R, 2 G719X, 5 L861Q, 3 combined S768I and G719X, and 1 singlet T790M. Clinical details were not available for all patients. A sensitising mutation was found in 51 of 92 patients (55.5%) under TKI therapy, where this was indicated on the request form; among these, an associated T790M mutation was found in 19 (37%) of patients. Several patients underwent multiple tests while they received TKI therapy; in two patients, the secondary mutation was detected prior to clinical progression.

Conclusions: We show here that EGFR plasma testing is perfectly suitable for clinical practice; it is highly specific and cost-effective due to rapid turnaround times, but the low sensitivity renders it complementary to tissue testing rather than a true surrogate.

Legal entity responsible for the study: N/A

Funding: None

Disclosure: All authors have declared no conflicts of interest.

131P Circulating tumor cells as liquid biopsy for castration resistant prostate cancer patients treated with cabazitaxel

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Background: Cabazitaxel (CBZ) has been shown to improve overall survival (OS) in metastatic castration resistant prostate cancer (mCRPC) patients (pts) and to overcome resistance to docetaxel (DOC). Circulating tumor cells (CTCs) can be useful tool for precision medicine. CTCs expression profiling before CBZ treatment could establish novel predictive biomarkers.

Methods: We prospectively enrolled 28 pts with mCRPC treated with CBZ 25 mg/mq q21 after DOC and abiraterone or enzalutamide. CTCs enrichment was assessed with Adna Test EMT/STEM. Expression analyses of AKR1C3, AKT2, ALDH1, AR, ARV7, EPCAM, FOLH1, MDK, PARP, MRP1, PIK3CA, POU5F1, PSCA, TUBB3, VIM, ACT, HPRT1 were analyzed using real time PCR. CTCs positive pts were defined when at least one marker among AKT2, AR, AR-V7, EPCAM, FOLH1, PSCA, PIK3CA was expressed. Progressive disease was defined according to PCWG2 criteria. Main endpoint was the correlation between CTCs expression profiling and outcome.

Results: Of these 28 pts, 18 (64%) had detectable CTCs before the starting of CBZ and 10 (36%) had undetectable CTCs. Detection of CTCs was associated with poor OS. However, no difference was observed for progression free survival (PFS). No correlation between CTCs assessment and PSA response rate was found. In addition, we subdivided pts according to median value of CTCs expression markers. Nine (50%) pts with ≥3 markers had a significant worse PFS compared to pts with <3 markers. Pts with ≥3 markers, reflecting heterogeneity of disease, had also a poor OS (Table).

Table: 131P

CTCs	Pts	PFS			OS		
		Median (months)	HR (95% CI)	*p*	Median (months)	HR (95% CI)	*p*
CTCs +	18/28	5.8	1.31 (0.58-3.04)	*p*=0.5220	9.7	7.03 (1.16-11.00)	***p*=0.0279**
CTCs -	10/28	7.0			–		
≥3 markers	9/18	2.5	3.59 (2.07-22.01)	***p*=0.0039**	3.9	5.92 (3.86-52.21)	***p*=0.0003**
<3 markers	9/18	10.1			16.6		

Conclusions: We prospectively confirmed a prognostic role for CTCs in mCRPC pts treated with CBZ and we also firstly showed the utility to characterize CTCs expression markers thanks to its potential predictive role. The identification of markers expressed

on CTCs may also provide additional therapeutic targets. More details on the prognostic impact of these biomarkers and *AR* status and mutations are under analysis and will be presented at meeting.

Clinical trial identification: IRSTB030

Legal entity responsible for the study: Ugo De Giorgi

Funding: Sanofi

Disclosure: All authors have declared no conflicts of interest.

132P Biomarker analysis using circulating tumor DNA in patients treated with sorafenib for advanced hepatocellular carcinoma

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Background: We aimed to investigate potential biomarkers in patients treated with sorafenib for advanced hepatocellular carcinoma (HCC) using circulating tumour DNA (ctDNA).

Methods: 155 patients who had started sorafenib between March 2014 and November 2016 were identified from a prospective biomarker cohort of Asan Medical Center, Korea. We quantified the concentration of ctDNA extracted from blood samples of each patient collected before sorafenib treatment and measured the copy numbers of vascular endothelial growth factor-A (VEGFA) in ctDNA. We also applied low depth whole genome sequencing from ctDNA to find copy number aberrations in HCC and employed Q-score, defined as a standard deviation regarding Z-scores of sequenced reads on each chromosome.

Results: Among 155 patients, 124 were finally included in the analysis. 82 patients achieved partial response, stable disease or non-CR/non-PD with sorafenib treatment (non-PD group) whereas 42 exhibited progressive disease (PD group). The PD group had significantly higher levels of ctDNA concentrations than the non-PD group (153.3 vs. 109.3 ng/mL; $p = 0.038$). Q-score of PD group was also higher than that of non-PD group but there was a borderline significant difference between two groups (6.10 vs. 3.80; $p = 0.058$). VEGFA copy number, which was available for only 41 patients, did not differ between PD ($n = 16$) and non-PD ($n = 25$) groups (2.56 vs. 2.48; $p = 0.467$). Divided into two groups based on the median value (119.7 ng/mL) of ctDNA concentrations, patients with high ctDNA had significantly shorter time to progression (TTP) (median, 2.3 vs. 4.1 months; $p = 0.025$) and overall survival (OS) (median, 4.5 vs. 14.8 months; $p < 0.001$) than those with low ctDNA. Similarly, patients with higher Q-score than median value of 4.12 had significantly worse TTP (median, 2.7 vs. 4.0 months; $p = 0.012$) and OS (median, 5.2 vs. 17.3 months; $p < 0.001$) compared to those with lower Q-score. After adjusting confounding factors by multivariate Cox regression analysis, the concentration of ctDNA and Q-score remained independent prognostic factors associated with both TTP ($p = 0.026$ and 0.042, respectively) and OS ($p < 0.001$ and $p = 0.001$, respectively).

Conclusions: Our results showed that ctDNA level and copy number aberrations represented by Q-score could be potential prognostic biomarkers in HCC patients treated with sorafenib.

Legal entity responsible for the study: Department of Oncology, Asan Medical Center, Seoul, Republic of Korea

Funding: None

Disclosure: All authors have declared no conflicts of interest.

133P Heparinase enables reliable quantification of circulating tumor DNA from heparin plasma samples by droplet digital PCR

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Background: Circulating tumor DNA has been highlighted as a potential "liquid biopsy", which can be used to identify prognostic and predictive alterations in oncology. Heparin is often used as plasma anticoagulant source for tumor marker analysis such as CA19.9 or CA15.3 but corresponds also to an inhibitory of PCR not enabling ctDNA detection. We aimed to evaluate the impact of heparinase addition on heparinized plasma samples to recovery the possibility of ctDNA analysis on samples initially dedicated for tumor markers analysis.

Methods: Plasma samples were collected in heparinized ($n = 194$) and EDTA ($n = 8$) tubes from hormone receptor-positive metastatic breast cancer (HR+MBC) patients resistant to aromatase inhibitor (AI) treatment ($n = 144$) and from newly diagnosed pancreatic adenocarcinoma (PA) patients ($n = 50$). *ESR1* and *KRAS* mutations were used as targets for ctDNA detection in HR+MBC and PA patients, respectively. ctDNA was detected by droplet digital PCR after an amplification step either without or with heparinase (H- and H+ respectively). PCR efficiency and ctDNA detection rate were compared between H- and H+ subgroups as well as with EDTA subgroup.

Results: Heparinase addition improved significantly PCR efficiency for 91/144 HR+MBC and 26/50 PA patients enabling ctDNA detection in 22/91 (24%) and 13/26 (50%) of these patients. Moreover, heparinase condition did not quantitatively and qualitatively alter the ctDNA detection for patients without heparin inhibition of PCR and comparable results for ctDNA detection were obtained between H+ and EDTA subgroups.

Conclusions: Heparinase addition allows removing the heparin inhibition on cfDNA amplification and to detect and quantify accurately ctDNA levels by dPCR in the heparinized plasma samples.

Legal entity responsible for the study: Rouen University Hospital

Funding: None

Disclosure: All authors have declared no conflicts of interest.

134P Circulating tumour DNA (ctDNA) in the clinical management of patients (pts) with advanced non-small cell lung cancer (NSCLC): A single centre experience

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Background: Circulating tumour DNA (ctDNA) is an emerging non-invasive method to guide personalised medicine in patients (pts) with advanced non-small cell lung cancer (NSCLC). The aim of this project was to assess the utility of ctDNA in routine clinical practice where tumour biopsy (Bx) was contraindicated or insufficient for genotyping.

Methods: A 73-gene cancer panel test using next generation sequencing for ctDNA profiling (Guardant360®) was offered at our institution to stage IV NSCLC pts. The reports obtained were discussed in a multidisciplinary Genomics Review Board (GRB) to assess potentially actionable genomic alterations and enrolment into clinical trials. All pts consented for prospective collection of demographic, clinical, and biomolecular data.

Results: Thirty advanced lung cancer pts were offered ctDNA testing. Histology included adeno- in 27 (90%) pts, squamous cell- in 2 (7%) pts, and small cell carcinoma in 1 (3%) pt. As assessed by baseline tumour Bx, EGFR status was mutant in 15 (50%) pts, wild type in 8 (27%) pts, and unknown in 7 (23%) pts. Activating EGFR mutations (mut) showed on original Bx at diagnosis were detected by ctDNA in 11 (73%) pts – lag-time 17 months (range 7-94). Primary EGFR mut were found in 2 pts with unknown EGFR status, allowing access to EGFR tyrosine kinase inhibitors (TKIs). Acquired T790M mut was found in 3 (20%) pts progressing on prior EGFR TKI, with the indication to receive Osimertinib. Only 1 pt with ctDNA-positive status for T790M mut received concomitant solid Bx which was negative for T790M mut. Other genomic alterations were detected in the overall population, more commonly involving TP53 ($n = 12$; 40%), NF1 ($n = 7$; 23%), MET ($n = 5$; 17%), BRAF ($n = 4$; 13%), PIK3CA ($n = 3$; 10%), BRCA 1/2 ($n = 3$; 10%), PDGFRA ($n = 3$; 10%), and AR ($n = 3$; 10%) genes. Critical review in the GRB was crucial in assessing genomic alterations of clinical significance.

Conclusions: Our study confirms the utility of ctDNA testing in advanced NSCLC pts where tumour Bx was not possible or insufficient for genotyping. Based on ctDNA, 5 pts received treatment with 1st- or 2nd-line EGFR TKIs while several pts were considered for clinical trial participation. Updated results of this ongoing study will be reported.

Legal entity responsible for the study: Sarah Cannon Research Institute UK

Funding: Guardant Health

Disclosure: R. Lanman, I. Faull: Affiliated to Guardant Health. All other authors have declared no conflicts of interest.

135P Genome-wide methylation analysis reveals a prognostic classifier for non-metastatic colorectal cancer (ProMCol)

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Background: Currently, pathological staging according to the tumor-node-metastasis system remains the gold standard for the prediction of patient survival in colorectal cancer (CRC) but this classification system provides insufficient information and therefore additional prognostic markers are needed.

Methods: A genome-wide methylation analysis was done for two independent cohorts of non-metastatic CRC patients (screening cohort n = 578 and validation cohort n = 308). Initially, genome-wide differentially methylated CpG sites between 34 pairs of tumor and normal mucosa tissue samples from the same patients were identified. A variable screening for prognostic CpG sites was performed in the screening cohort using marginal testing based on the Cox model and subsequent adjustment of the *p*-values via independent hypothesis weighting (IHW) using the difference between tumor and normal mucosa tissue as auxiliary covariate. From the 1000 CpG sites with the smallest adjusted *p*-value, the 20 CpG sites with the smallest Brier Score for 3-year overall survival (in the screening cohort) were selected. Applying principal component analysis on these CpG sites, we derived a methylation-based classifier for the prognosis of non-metastatic CRC (ProMCol).

Results: The ProMCol classifier was independently validated in the validation cohort, where it showed a significant reduction in the Brier score. Regarding the three year survival, the prediction error was reduced from 0.132 (calculated only with clinical variables), to 0.124 (combination of clinical variables with ProMCol classifier). An additional replication analysis showed that the ProMCol classifier was significantly associated with overall survival (OS) of non-metastatic CRC patients in the screening (HR = 0.22, 95%CI=0.13-0.35, *p*=6.2E-10) and the validation cohort (HR = 0.40, 95%CI=0.22-0.74, *p*=0.003), adjusted for standard clinical factors. Patients with a high methylation status, represented by higher values of the ProMCol classifier, showed a better prognosis for OS than patients with a low methylation status and lower ProMCol classifier values.

Conclusions: The usage of the ProMCol classifier could improve the prognostic accuracy for non-metastatic CRC patients.

Legal entity responsible for the study: Barbara Burwinkel, German Cancer Research Center

Funding: German Research Council, German Federal Ministry of Education and Research

Disclosure: All authors have declared no conflicts of interest.

136P Epigenetic biomarkers in breast cancer: Preliminary results from H3K27m3 assessment in endocrine-treatment resistance

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Background: Breast cancer (BC) is an important cause of morbidity and mortality. Most BC are hormone-receptor positive and can be treated with endocrine treatment (ET), until resistance or toxicity is developed. Specifically, H3K27m3, an epigenetic marker of gene repression, has been associated with prognosis in ET resistant BC. Herein, we aim to further understand its potential role as predictive marker of ET resistance before exposure to treatment.

Methods: A cohort of BC patients diagnosed between 1995 and 2002 at our institution were enrolled after informed consent. Expression of H3K27me3 was determined by immunohistochemistry (IHC) in formalin fixed paraffin embedded tissues. GenASIs^{TM} software was used to assess cell-positivity using a custom profile from positive control. Pre-specified conditions: $\geq$ 5 frames $\geq$ 3000 cells analyzed/case. SPSS v24 was used for statistical purposes.

Results: A total of 102 cases were assessed for H3K27me3 immunoexpression. Median of 6 frames/case (range 5-10) and 3311 cells/case (range 3017-5292) were obtained. Of the total cases analyzed, a median of 80% of cells showed positivity (range 9-100%). Using a negative/positive 50% cut-off, 81% were considered positive (pos.). The analyzed cohort displayed a median age of 60 years (33-82 years), 89% were classified as ductal carcinoma (DC) and 38% were grade 3. Concerning IHC subtyping, 43% classified as Luminal A-like, whereas 57% Luminal B-like. Around 66% of the cases evaluated for H3K27me3 expression were treated with adjuvant Tamoxifen exclusively. BC cases with H3K27me3 50-60% positivity were associated with higher cancer-related death (CI 95% 1.10-34.38, p = 0.05), although not reaching significance. Grade 3 BC significantly associated with increased risk of death (p = 0.024). An intermediate H3K27me3 expression (60-70% pos.) was observed in non-DC BC (CI 95% 1.42-13.92, p = 0.04).

Conclusions: In this preliminary retrospective cohort, H3K27m3 positivity was not found to be a pre-treatment endocrine resistance biomarker. However, statistical trends were observed between H3K27m3 expression and increased cancer-related death risk. Thus, further studies with extended cohort of patients are warranted.

Legal entity responsible for the study: Cancer Biology and Epigenetics Group, IPO Porto Research Center (CI-IPOP), Portuguese Oncology Institute of Porto (IPO Porto), Porto, Portugal

Funding: None

Disclosure: All authors have declared no conflicts of interest.

137P Bioinformatic estimate of biomarker-positive populations in genomics-driven trials using precision trial designer (PTD)

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Background: Trials that prospectively accrue based on genetics are powerful methods to test hypotheses in precision oncology, but are often difficult to conduct due to the rarity of biomarker-positive cases. This is mitigated in umbrella trials that maximize accrual by testing many hypotheses. However, multiple treatment arms frequently generate conflicting treatment allocations due to simultaneous actionable mutations; the allocation algorithm should be planned based on relative mutation frequencies to accurately estimate sample size and dropout rates. Large sequencing projects like the TCGA could be exploited but proper tools are lacking.

Methods: We developed Precision Trial Designer (PTD), a bioinformatic tool that simulates genomically-defined cohorts by iteratively sampling patient data from mutation databases (e.g. TCGA) and provides essential parameters to plan biomarker-driven trials using survival or response-rate endpoints. To show its potential, we simulated a 10-arm imaginary trial on multiple cancers, based on the Molecular Analyses for Personalized medicine (MAP) consensus. We then validated our approach by comparing simulated and real data from the SHIVA01 clinical trial.

Results: In the MAP trial, PTD predicted $\geq$1 actionable alteration in 73% patients and 32% conflicts. To adequately power each arm, we found the optimal rule that maximizes accrual (ALK inhibitors first, AKT inhibitors last) and propose various designs. In the SHIVA01 simulation, combinatorial point mutations were correctly predicted (18.9%, 95%CI 15.7-22.1 simulated vs 15.3%, 11.8-18.7 real), whereas PTD slightly overestimated copy number alterations (36.3%, 31.6-41 simulated vs 25.6%, 21.4-29.7 real), a predictable gap due to different detection techniques. Overall, 50.8% (46.2-55.7) cases were predicted as biomarker-positive, vs 37% (32.5-41.7) real. The relative contribution of each pathway of treatment (RAS/MEK, PI3K/MTOR) was conserved (47.8%, 41.7-53.9 and 25.8%, 19.9-31.5 simulated vs 53.1%, 95%CI 48.3-57.9 and 31.6%, 27.2-36.1 real, respectively).

Conclusions: PTD predicts combinatorial mutation frequencies with acceptable approximation and overcomes pressing issues in designing precision trials.

Legal entity responsible for the study: Luca Mazzarella

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Disclosure: All authors have declared no conflicts of interest.

138P Detection of microsatellite instability (MSI) in colorectal cancer samples with the automated Idylla MSI Test

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Background: Detection of microsatellite instability (MSI) is recommended for all colorectal cancer (CRC) patients. Current clinical reference methods to detect MSI stain for mismatch repair proteins or analyze frequently mutated DNA repeat regions. The Idylla MSI Test is being developed using a unique set of novel biomarkers (Zhao et al. 2014; eLife) capable of faster detection with greater specificity and selectivity compared to current methods.

Methods: To assess the suitability of the novel marker set to detect MSI status in CRC, we profiled 8 or more markers in 870 CRC samples. Several clinical sites and different ethnic groups (Afro American, Caucasian, East-Asian, Hispanic and Indian) were included to assess robustness of marker selection. Repeat length was determined on FFPE DNA by PCR followed by melting curve analysis. Two-hundred and one samples were additionally screened with a reference methodology for MSI detection (Promega MSI analysis system).

Results: Hundred fifty-three samples (17.6%) were classified as MSI-H and 693 samples (79.7%) as MSS with the novel set of biomarkers, while 24 samples (2.8%) could not be classified. Concordance analysis was performed on 201 samples. The overall percent agreement with results available for both methods (173/201) was 93.6%. 11/173 (6.4%) were scored MSI-H for Idylla and MSS for the reference method; conversely no MSI-H cases for the reference method and MSS for Idylla were detected. 24/201 (11.9%) samples failed with the reference method, even after repeat testing, while only 8/201 (4.0%) samples failed with the Idylla methodology.

Conclusions: This study on a diverse set of CRC samples successfully demonstrated the validity of the novel MSI biomarkers to discriminate between MSI-H and MSS status. The Idylla MSI Test is currently under development on the most performant markers. Compatibility with the fully integrated Idylla platform will allow providing accurate and reliable results, with actionable results generated within 150 minutes from just one tumor FFPE slice (no reference sample required).

Legal entity responsible for the study: Biocartis NV

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139P Gene expression BIRC5, Erb-b2/Her2-neu, ESR1, PGR1, MMP11, MDR1, MRP1, MXR at the CTCs in the primary breast cancer

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Background: Distant metastases are the main cause of death of patients with breast cancer. The substrate for the development of metastasis are the circulating tumor cells (CTCs). Determination of the expression of tumor-specific genes gives a more complete picture of the course of the tumor process.

Methods: Using PCR technology in real-time, gene expression studied BIRC5, Erb-b2/Her2-neu, ESR1, PGR1, MMP11, MDR1, MRP1, MXR at the CTCs in the surgical and adjuvant treatment of 56 cases primary non-metastatic breast cancer.

Results: In 33 (59%) prior to surgery functionally active in the CTCs-enriched peripheral blood, samples expressing the targeted range of different genes have been found. Simultaneous expression of targeted genes detected in 15 (26.8%). The highest levels of expression of the genes identified for BIRC5 1.2013 ± 0.193965 (min – 0.0017; max – 10.7083) and-Erb-b2/Her2-neu 1.6886 ± 0.0939 (min – 0.1032; max – 17.4401). Expression of ESR1, PGR1 were determined in 23 patients (42.5%). Expression family of ABC transporters detected in 14 (25%). After the operation was observed decrease in the number of CTCs and including functionally active to 13 cases (23.2%), but the CTCs data determined high levels of gene expression BIRC5, c-Erb-b2/Her2-neu, and MXR. During adjuvant, treatment with anthracyclines observed decrease in the level of gene expression BIRC5, ESR1, PGR1 at the CTCs in 7 patients. However, in 6 samples marked increase in the level of gene expression MDR1, MRP1. In the course of a taxane therapy in combination with trastuzumab in a group of patients of the 14 people there was a decrease, and the complete disappearance of the expression of a-Erb-b2/Her2-neu in 9 people, but in 5 patients there was a significant increase in the level of expression of targeted genes-Erb-b2/Her2-neu, BIRC5 and MXR. Expression of the gene in MMR11 CTCs-positive samples was determined at a high level, but significant reduction in the course of chemotherapy has not been determined.

Conclusions: The data indicate a high diagnostic, prognostic and predictive value of determining the functional activity of the CTCs on the basis of determining the dynamics of gene expression of tumor progression at the stage of planning treatment of breast cancer.

Legal entity responsible for the study: Educational Establishment "Vitebsk State Order of Peoples' Friendship Medical University"

Funding: Belarusian Republican Foundation for Fundamental Research

Disclosure: All authors have declared no conflicts of interest.

140P Metabolic syndrome and inflammation in castration resistant prostate cancer (CRPC) patients (pts) treated with abiraterone (abi) and enzalutamide (enza)

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Background: Metabolic syndrome (MS) and inflammation (INF) alterations are hallmarks of cancer progression. The study aimed to firstly assess the relationship between MS and INF and its impact on progression-free/overall survival (PFS/OS) in CRPC pts.

Methods: We retrospectively evaluated CRPC pts treated with abi and enza in 7 Italian Institutes between March 2011 and October 2016. MS was defined by modified Adult Treatment Panel III criteria, and INF characterized by the presence of at least 1 of these criteria: NLR≥3, elevated VES or C-reactive protein (CRP) levels.

Results: Eighty-three of 551 pts evaluated (15%) met MS criteria at baseline, whereas for 40 (8.5%) this occurred during treatment. No significant difference of MS incidence and cardiometabolic toxicities were reported between abi or enza. Pts with MS (MS+) showed a greater INF profile compared to MS- (79% vs 28%, $p < 0.0001$). We observed NLR≥3 in 70.2% of MS+ vs 38% of MS-, $p < 0.0001$, and median values of VES and CRP higher than upper normal limit (UNL) in MS+ vs MS- (53 vs 15, $p < 0.0001$, UNL<30 and 15 vs 3.3, $p < 0.0001$, UNL<5mg/L, respectively). Median PFS and OS were associated with baseline MS and INF and their combination defined clinically high- and low-risk prognostic groups (MS+/INF+ vs MS-/INF-) (Table). Multivariate analysis confirmed that MS was independently associated with PFS (HR = 2.07, 95%1.03-4.18 p = 0.041) and OS (HR = 4.87, 95% CI 2.36-10.03, $p < 0.0001$).

Conclusions: The presence of MS is strongly associated with INF. Pre-treatment identification of MS and INF alterations may represent an available and easy to perform tool for a better prognostication of CRPC pts treated with abi or enza. A prospective evaluation is warranted.

Table: 140P Univariate analyses of progression-free survival (PFS) and overall survival (OS) according to Metabolic Syndrome (MS) and In˜ammation (INF) status

	N. events/ total atient	Median PFS (months) (95% CI)	p	HR (95% CI)	p	N. events/ total atient	Median OS (months) (95% CI)	p	HR (95% CI)	p
Overall	407/551	7.4 (6.4-7.8)				308/551	17.6 (15.5-19.0)			
Baseline MS										
No	337/468	8.3 (7.4-9.2)		1.00		247/468	19.0 (17.4-21.6)		1.00	
Yes	70/83	3.7 (3.5-4.1)	<0.0001	2.77 (2.12-3.61)	<0.0001	61/83	6.9 (5.4-9.8)	<0.0001	3.43 (2.56-4.58)	<0.0001
Baseline INF										
No	179/231	8.5 (7.4-9.2)		1.00		141/231	18.8 (15.9-21.8)		1.00	
Yes	98/133	4.5 (3.7-5.9)	0.002	1.48 (1.15-1.90)	0.002	82/133	11.2 (8.4-16.8)	0.0003	1.66 (1.26-2.18)	0.0003
Combination MS+INF										
MS- & INF-	167/218	9.0 (7.6-9.2)		1.00		130/218	20.4 (16.5-24.0)		1.00	
MS- & INF+	60/85	6.0 (3.9-9.8)		1.25 (0.93-1.68)		46/85	18.0 (11.1-22.4)		1.25 (0.89-1.76)	
MS+ & INF-	12/13	3.5 (1.8-4.7)		3.77 (2.07-6.84)		11/13	6.5 (3.0-11.2)		3.80 (2.04-7.09)	
MS+ & INF+	38/48	3.7 (2.9-4.0)	<0.0001	2.70 (1.88-3.89)	<0.0001	36/48	6.3 (4.7-8.6)	<0.0001	4.04 (2.75-5.93)	<0.0001

Legal entity responsible for the study: Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) Srl – IRCCS

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141P Ischemic stroke and cancer correlation: A stroke unit experience

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Background: Cancer (Cr) and ischemic stroke (IS) are common causes of death in high-income regions. Cr patients present a higher probability of developing thromboembolic events, particularly IS. Measurable objective parameters may be helpful stating a neoplastic etiology: High D-dimer (DD) levels; C-reactive protein (CRP); Neutrophil–lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) express the severity of inflammation relating it to etiology and prognosis. Single centre retrospective study analyses patients with IS and active solid Cr (NG) with purpose of identifying clinical, laboratorial and imagological features that differentiate this from a control group (CG) without Cr.

Methods: Patients with IS admitted in a Stroke Unit from 01/2009 to 12/2014. Active cancer identified in clinical process. Transient ischemia, haemorrhagic strokes and other diagnosis excluded. For CG an age and gender matching patient was chosen. Clinical, analytical and imagological features were compared between groups. Statistical analysis using the SPSS Statistics V22.

Results: Out of 603 consecutive patients with IS, 48 (7.9%) had active solid Cr, 16 diagnosed during diagnostic work-up for IS, 24 before and 8 in the year after. Male predominance: 30 patients (62,5%). 14: metastatic disease. Most frequent Cr diagnosed were prostate and bladder (12,5% each); colon(10%) and lung(8,3%). Cardioembolism was the main subgroup in both (26 NG; 24 CG). Imagiologic pattern was similar in both groups. NG had increased laboratorial values compared to CG: LDH 602 vs 501 U/L (p 0,04); CPR 3,2 vs 1,8 mg/dL (p 0,11) and DD 0,85 vs 0,7ug/mL (p 0,28). Average NLR and PLR: 5,4 and 161,6 NG vs 2,34 and 104,1 CG ($p < 0,01$ and 0,03 respectively). NG and CG average NIHSS was 6,3 vs 4,9 (p 0,18) and mRs was 2,75 vs 1,95 (p 0.019) respectively. Higher NLR and PLR were associated with worse outcomes (higher NIHSS and mRs score).

Conclusions: Although Cr is a rare cause of stroke, it should not be devalued. There are several clinical, laboratory and imagiological signs of underlying neoplastic disease that should be considered, since they may promote an earlier diagnosis and approach to this pathology. Future prospective studies should be started in order to validate some of this parameters as indicators of subjacent neoplastic disease.

Legal entity responsible for the study: Mariana Rodrigues

Funding: None

Disclosure: All authors have declared no conflicts of interest.

142P longitudinal exploratory analysis of prior- surgery everolimus circulating and clinical biomarkers in locally advanced and metastatic renal cell carcinoma patients (RCC)

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Background: If many drugs are available in RCC, we lack predictive biomarkers of disease recurrence or progression for personalized treatment. Circulating biomarkers (CB) are attractive candidates for disease monitoring. Longitudinal assessment of CB was performed in the NEORAD clinical trial (NCT01715935).

Methods: Locally advanced (LA) and metastatic (M) patients with clear cell or papillary RCC received 6 weeks prior-nephrectomy everolimus (Ev). CB assessed were: angiogenesis factors: VEGF-A, VEGFR-1&2, bFGF, SDF1, PlGF; CEC; CTC; HSC; immune cells: CD45, CD14+VEGFR-1/Tie2, Treg, IL-6. Clinical/histological (CH): ECOG-PS, tumor burden (TB), % necrosis, % sarcomatoid. Exploratory analysis (EA): CB and CH (prior to Ev, D22, D42, 4 weeks post-nephrectomy (+ 4 weeks if Ev resumed in M pts) in PD vs non-PD pts used Bayesian Model Averaging (BMA) and regularized Cox regression (LASSO). Three modeling strategies were compared for robustness.

Results: 25 patients were included: LA = 14, M = 11. In LA and M cohorts, respectively 2 and 9 pts exhibited progression during the 12m post-surgery follow-up period. Most important predictors upon EA (by order): tumor burden, VEGF-A, LA/M, VEGFR-2, % necrosis, IL-6, VEGFR-1, age, PlGF. Higher TB at baseline and % necrosis were associated with increased risk of 6m post-nephrectomy progression. TB, IL-6, VEGF-A, VEGFR-1&2 exhibited nonlinear relationships suggesting complex underlying pathophysiological mechanisms involved in response to Ev, and are currently explored. Reduced VEGFR-2 at D42 was associated with worse PFS in both cohorts. Upon BMA and LASSO, % necrosis and TB were among the most retrieved predictors prior to nephrectomy, whereas CD45 and CD34 + 45-146+ at 4 weeks post-nephrectomy were the best CB predictors. No significant change in monocyte populations and in Treg was observed.

Conclusions: VEGF related CB, TB and % necrosis were the best candidates to discriminate PD- vs non-PD in LA and M pts. Extensive analysis of data collected using robust non-linear models could contribute to improve our understanding of mechanisms involved and suggest predictive biomarkers to be validated.

Clinical trial identification: NCT01715935

Legal entity responsible for the study: ARTIC

Funding: Novartis

Disclosure: All authors have declared no conflicts of interest.

143P A comparison of treatment recommendations by molecular tumor boards worldwide

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Background: Precision oncology holds promise to improve patient outcome. Yet, a benefit of personalized therapy in comparison to standard therapy has not been shown in prospective trials. We asked molecular tumor boards (MTB) worldwide to make treatment recommendations for sample patients to assess standards and differences in the precision oncology approach.

Methods: 4 fictional patients with various degrees of genomic information (mutation, gene expression, copy number and gene fusion data, somatic and germline events) were created. A questionnaire was designed to identify methods and structures of the respective molecular tumor board's recommendation process. 29 molecular tumor boards from 9 countries were identified and asked to participate in the survey between August 2016 and March 2017. A qualitative interpretation of the results was performed.

Results: 5 MTBs from 4 countries completed the questionnaire and provided therapy recommendations. An identical treatment recommendation by all 5 MTB was not made for any one of the patients. In only one patient an overlapping treatment recommendation was made by three MTBs. Heterogeneity was larger for patients with more complex genomic information. The availability of clinical trials did not influence the recommendation heterogeneity. The setup of MTBs showed similarities in participating specialties (e.g. medical oncology, pathology, molecular biology), duration of discussion, testing methods and number of discussed patients. Differences were seen in the interpretation process. Further differences were identified in the interpretation of germline aberrations and interpretation of variant allele frequency. Comments by MTBs helped to identify minimum reporting standards for genetic testing.

Conclusions: Several differences in treatment recommendations were observed. In cases with obvious recommendations there was higher concordance among assessments. However, differences in treatment recommendations were observed in complex cases, and such heterogeneity contributes to the complexity of precision oncology. Larger studies are necessary for rational and stepwise development of principles and practice of MTB procedures.

Legal entity responsible for the study: Damian Rieke

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144P Identification of germline mutation using 30-gene sequencing and clinical characteristic of Chinese with hereditary breast cancer

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Background: With the recent discovery of other breast cancer susceptibility genes (e.g. *CDH1*, *ATM*, *CHEK2*, *PALB2*, *RAD50)*, molecular diagnosis of hereditary breast and ovarian cancers (HBOC) using multigene panels could help to identify other moderate/low penetrance genes in patients who tested negative for *BRCA* mutation. However, the clinical management of these cancer predisposition genes have not been clearly defined, therefore only *BRCA1* and *BRCA2* are routinely included in the genetic screening. In view of the differences in the mutation spectrum across ethnicity, it is important to identify other HBOC genes to estimate the associated breast cancer risk in Chinese.

Methods: High-risk breast cancer patients who were negative for *BRCA1*, *BRCA2*, *TP53* and *PTEN* were selected from the Hong Kong Hereditary Breast Cancer Family

Registry between 2007-2016. In the study, 745 patients were subjected to 30-gene panel by next-generation sequencing (Color Genomics). All detected pathogenic mutations were further validated by bi-directional DNA sequencing. The sequencing data was co-analyzed by our in-house developed bioinformatics pipeline.

Results: Thirty-five pathogenic variants were identified in this series (4.7%), which correspond to 11 different cancer predisposition genes. Majority of the carriers (74.29%) had early-onset of breast cancer (age <45), 42.86% had ³ 2 family members with cancer and 17.14% were triple-negative. The most common mutated genes were *PALB2* (1.21%), *RAD51D* (0.94%) and *ATM* (0.67%). However, the cancer risk of *RAD51D* in breast cancer warrants further investigation. Moreover, over 28% of patients had a variant of unknown significance (VUS) in these genes (excluding *BRCA1, BRCA2, TP53* and *PTEN*), which account for 183 types of VUS. Data from large-cohort studies and international consortiums will help to define the pathogenicity and clinical interpretation/management of the variants.

Conclusions: Our findings suggested that detection of *PALB2* should be included in the genetic test panel in Chinese with breast cancer. Multigene panel testing is an efficient tool in the diagnosis of HBOC, this could help patients to understand the cancer risk and aid the development of effective treatments.

Legal entity responsible for the study: Ava Kwong

Funding: None

Disclosure: All authors have declared no conflicts of interest.

145P Selecting patients with metastatic colorectal cancer for treatment with temozolomide using proteomic analysis of MGMT

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Background: Temozolomide (TMZ) is a standard treatment for melanoma and glioblastoma and it has shown limited but encouraging activity in patients with metastatic colorectal cancer (mCRC). In multiple cancer types, the DNA repair protein O^6-methylguanine-DNA methyltransferase (MGMT) is a resistance marker for TMZ; MGMT promoter methylation is associated with loss of MGMT expression and response to TMZ. We hypothesized that mCRC patients whose tumors expressed quantities of MGMT protein below a pre-defined cutoff would have better outcomes on TMZ than patients with MGMT expression above the cutoff. To test our hypothesis, we assessed MGMT by mass spectrometry in the tumor samples of patients with refractory mCRC and MGMT promoter methylation receiving TMZ.

Methods: Archived formalin-fixed, paraffin-embedded tissue sections were obtained from 24 patients from two phase 2 trials. A pathologist marked the tumor areas, which were microdissected and solubilized. In each tumor sample, multiple protein biomarkers including MGMT were quantified with selected reaction monitoring mass spectrometry. An MGMT cutoff of 200 amol/ug was based on the limit of quantitation from a concentration curve. The Mantel-Cox log-rank and the Fisher's exact tests were used for survival comparisons.

Results: MGMT protein was detected in 13 of 24 (54.2%) colorectal tumor samples (range: 229.3-784.8 amol/μg). The overall response rate was 29%. Patients with MGMT protein levels below a cutoff of 200 amol/ug (n = 11) had a notably higher response rate than patients with MGMT levels above the cutoff (64% vs. 0%; p = 0.001 Fisher's test). Also a longer progression-free survival was observed (4.3 vs. 1.6 months, HR = 0.36, 95% CI = 0.13-1.10, p = 0.054). Results for overall survival were consistent but not statistically significant (8.9 vs 6.9 months, HR = 0.55, p = 0.221).

Conclusions: Patients with mCRC whose tumors expressed low or undetectable levels of MGMT protein had better outcomes following TMZ treatment than their counterparts. Quantitative proteomic analysis of MGMT could potentially be used to select CRC patients for TMZ treatment. The results of validation studies are forthcoming.

Legal entity responsible for the study: NantOmics

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Disclosure: S. Schwartz, F. Cecchi, Y. Tian, K. Scott, T. Hembrough: Employee at NantOmics. All other authors have declared no conflicts of interest.

146P Predicting response to chemotherapy in gastric cancer patients randomized to docetaxel: A reevaluation of the ITACA-S trial

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Background: No predictive biomarker for chemotherapy has been validated for clinical use. Clinical studies suggest tumor expression of the proteins class III β-tubulin (TUBB3) and thymidine phosphorylase (TYMP) predict resistance to taxane and response to 5-FU, respectively. Immunohistochemical definitions of protein status vary widely. We evaluated relationships between survival and expression of TUBB3 and TYMP as quantitated by mass spectrometry in the archived tumor samples of 247 patients from the Intergroup Trial of Adenocarcinoma of the Stomach (ITACA-S). Patients had been randomized to monotherapy with 5-FU/LV or to FOLFIRI plus docetaxel and cisplatin.

Methods: Gastric tumor tissues were microdissected and solubilized for proteomic quantitation of 45 protein biomarkers. The cutoff for TUBB3 (750 amol/μg of total protein) was predetermined based on the assay's limit of detection. An experimental cutoff for TYMP (1335 amol/ug) was derived in the 5-FU/LV-treated patients using Monte Carlo 2-fold cross-validation. The Mantel-Cox log-rank test was used for survival comparisons.

Results: Among gastric cancer (GC) patients treated with docetaxel-containing chemotherapy (n = 125), those with TUBB3 protein levels below the cutoff had a longer median overall survival (mOS) than patients with TUBB3 levels above the cutoff (1563 vs 886 days, p < 0.04). TUBB3 level made no difference in survival among patients who received 5-FU/LV (p = 0.64). Of note, among patients with high TUBB3 levels, those treated with 5-FU/LV survived 3 years longer than patients treated with docetaxel (mOS = 1991 vs 886 days, p = 0.048). 5-FU/LV-treated patients (n = 122) with TYMP protein expression above the cutoff survived longer than those with lower TYMP levels (mOS: 2362 vs 1062 days, p < 0.02). A combination of TUBB3 and TYMP expression predicted the longest survival in patients treated with FOLFIRI plus docetaxel (p < 0.001).

Conclusions: Quantitative proteomic analysis identified subsets of trial patients who benefitted from specific adjuvant chemotherapy regimens. Personalized chemotherapy based on quantitated TYMP and TUBB3 is promising and warrants broader evaluation.

Legal entity responsible for the study: NantOmics, LLC

Funding: IRCCS and NantOmics, LLC

Disclosure: F. Cecchi, S. Schwartz, S. Sellappan, T. Hembrough, Y. Tian: Employee at NantOmics. All other authors have declared no conflicts of interest.

147P The nationwide cancer genome screening project in Japan SCRUM-Japan GI-SCREEN: Efficient identification of cancer genome alterations in advanced pancreatic cancer

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Background: We have conducted the Nationwide Cancer Genome Screening Project in Japan since April 2015 using Next Generation Sequencing in cancers of digestive system, called as the SCRUM-Japan GI-SCREEN. In this presentation, we show the result of advanced pancreatic cancer (aPC).

Methods: This study is ongoing with the participation of 20 major cancer centers. Patients who plan to or receive systemic chemotherapy were eligible. DNA and RNA were extracted from FFPE tumor samples and were analyzed by the Oncomine Cancer Research Panel (OCP) which allows to detect gene mutation, copy number variant (CNV) and fusions across 143 genes in a CLIA certified CAP accredited laboratory. 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. In this presentation, we show the results of aPC cohort.

Results: As of 31st October 2016, a total of 179 aPC samples were analyzed. The sequence with the OCP was successfully performed in 120 (67.0%). Out of 120 patients, the proportion of location of tumor and histology type is follows; Ph = 44%, adenocarcinoma 97%. The proportion of procedure for sample collection is follows; surgical resection 35.0%, needle biopsy 38.3%, EUS-FNA 20.0%, other 5.8%, and unknown 0.8%.The frequently detected mutations (> 10%) in 120 samples of which results were available were KRAS (93%), TP53 (63%), CDKN2A (12%), and SMAD4 (11%). Other

important/druggable mutations were GNAS, BRCA2, and ATM (3%, each). Most frequently detected CNVs (≥ 7copies) was MYC (3%), and no gene fusion was detected.

Conclusions: This nationwide screening system is efficient to detect rare gene alterations in aPC. Alterations in potentially druggable genes were limited in aPC, but homologous recombination repair genes were attractive target. This novel knowledge provides an intriguing background to investigate new target approaches and represents a progress toward more precision medicine.

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Legal entity responsible for the study: SCRUM-Japan GI-SCREEN

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BREAST CANCER, EARLY STAGE

1480 Phase III evaluating the addition of fulvestrant (F) to anastrozol (A) as adjuvant therapy in postmenopausal women with hormone receptor positive HER2 negative (HR+/HER2-) early breast cancer (EBC): Results from the GEICAM/2006-10 study

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Background: F is a selective estrogen receptor degrader for HR+ advanced breast cancer patients (pts). We designed this trial to compare A vs. A in combination with F (A+F) to address the hypothesis that a complete estrogen blockade can prevent resistance to aromatase inhibitors in the adjuvant setting.

Methods: This was a multicenter, open label, phase III study in which HR+/HER2- EBC postmenopausal pts were randomized 1:1 to A for 5 years (y) or A+F (A concurrently with F 250mg/4 weeks for 3y followed by 2y of A). Pts were stratified for prior chemotherapy (yes/no); number of positive lymph-nodes (0/1-3/≥4); HR status (both positive/one positive) and site. Primary objective was disease-free survival (DFS). To detect an absolute 5-y DFS increase of 3% (90% A, 93% A+F) a sample size of 2716 evaluable patients was required. On 2010, when the negative results of the FACT trial were made available, the financer decided to stop the study support after the inclusion of 872 pts.

Results: From January 2008 to June 2010, 437 pts were randomized to A and 435 to A+F. Pts characteristics were well balanced between arms; median age was 62 y (40-86), 46.9% were N0, 89.5% ER+/PgR+ and 68.2% had received prior chemotherapy. Treatment was completed as planned by 72.5% and 48.5% of A and A+F pts. Median relative dose intensity was 99% for A (both arms) and 81% for F. Most relevant G2-3 toxicities (>5% in either arm) with A vs. A+F were hypertension (13.2%; 9.9%), fatigue (5.2%; 11.8%), LDL-Cholesterol increase (9.4%; 5.3%), osteoporosis (5.5%; 6.9%) and musculoskeletal bone/joint pain (26.3%; 29.4%). After a median follow-up of 6.3y, the proportion of pts disease free at 5y was 90.99% (A 90.77%, A+F 91.25%, D = 0.48%, p = 0.357); 9.4% had BC relapse (A 10.5%; A+F 8.3%, D = 2.2%) and 4.3% had secondary tumors (A 3.9%; A+F 4.6%). Survival and breast cancer-specific survival were not reached.

Conclusions: The GEICAM/2006-10 study failed to demonstrate a statistically significant increase in DFS adding F to A as adjuvant therapy, though no formal conclusion can be extracted from this trial due to the F administered dose and the actual trial sample size.

Clinical trial identification: NCT00543127

Legal entity responsible for the study: GEICAM Spanish Breast Cancer Group

Funding: Astra Zeneca Astra Zeneca Astra Zeneca Astra Zeneca

Disclosure: M. Martin Jimenez: Speaker honoraria and AstraZeneca advisory boards participation. J.M. Baena-Canada: Consulting/relationship advice for AstraZeneca. M. Muñoz: Advisory Board from AstraZeneca. All other authors have declared no conflicts of interest.

1490 Neratinib after trastuzumab (T)-based adjuvant therapy in early-stage HER2+ breast cancer (BC): 5-year analysis of the phase III ExteNET trial

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Background: In the Herceptin Adjuvant (HERA) trial, 24% of patients (pts) who received T for 1 year (y) had a disease recurrence at 11 y follow-up. The primary analysis of the ExteNET trial, performed after 2 y follow-up, showed that a 1-y course of neratinib after T-based adjuvant therapy significantly improved invasive disease-free survival (iDFS) *vs* placebo in early-stage HER2+ BC (HR 0.67; 95% CI 0.50–0.91; p = 0.0091) [Chan et al. *Lancet Oncol* 2016]. We now report updated 5-y efficacy findings.

Methods: ExteNET is an international, multicenter, randomized, double-blind, placebo-controlled phase III trial. Pts received oral neratinib 240 mg/d or placebo for 1 y. After 2 y, randomized pts were asked to re-consent to collection of data concerning disease recurrences and survival from medical records for a further 3 y. The preplanned 5-y analysis was by intention-to-treat (ITT). Non-consenting pts were censored at their last physical examination. Primary endpoint: iDFS. HR (95% CI) were estimated using Cox proportional-hazards models. Data cut-off: March 2017. Clinicaltrials.gov: NCT00878709.

Results: ITT population comprised 2840 pts (neratinib, n = 1420; placebo, n = 1420); 53 pts died during the initial 2-y follow-up. Among 2787 available pts, 2117 (76%) re-consented to additional follow-up (neratinib, n = 1028; placebo, n = 1089). Updated results after a median follow-up of 5.2 y are shown below. Secondary efficacy endpoints were supportive of the primary analysis.

Table: 1490

	n	Estimated 5-y iDFS rate, % Neratinib	Placebo	HR (95% CI)	P value
ITT	2840	90.2	87.7	0.73 (0.57–0.92)[a]	0.008
Centrally confirmed HER2+	1796	90.4	88.2	0.74 (0.55–1.00)	0.047
HR +[b]	1631	91.2	86.8	0.60 (0.43–0.83)	0.002
HR–[b]	1209	88.8	88.9	0.95 (0.66–1.35)	0.762
Completed T ≤ 1 y of randomization	2297	89.7	86.5	0.70 (0.54–0.90)	0.006

HR, hormone receptor; [a]Stratified analysis; [b]Stratification factor.

Conclusions: 1 y of neratinib after T-based adjuvant therapy significantly improves iDFS at 5 y in pts with early-stage HER2+ BC, with a long-term sustained effect. A protocol-specified subgroup analysis suggested greater benefit in HR+ pts. Overall survival data are not yet mature.

Clinical trial identification: NCT00878709

Legal entity responsible for the study: Wyeth, Pfizer and Puma Biotechnology

Funding: Puma Biotechnology

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151PD Efficacy and safety of biosimilar ABP 980 compared with trastuzumab in HER2 positive early breast cancer

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Background: Analytical, functional, and pharmacokinetic similarity between ABP 980 and trastuzumab (TRAS) has been demonstrated. Here we report the results of primary efficacy analysis in the corresponding clinical study.

Methods: The objective of this randomized, multicenter, double-blind study was to compare ABP 980 with TRAS on pathologic complete response (pCR) in women with HER2 positive early breast cancer. After run-in anthracycline-based chemotherapy, patients were randomized 1:1 to intravenous ABP 980 or TRAS plus paclitaxel Q3W for 4 cycles. Patients had to complete a full cycle of run-in therapy to be eligible for randomization. Patients continued to the adjuvant phase on IP Q3W for up to 1 year. The co-primary endpoints were risk difference (RD) and risk ratio (RR) of pCR in breast tissue and axillary lymph nodes of tumor samples. Clinical similarity was confirmed if the 2-sided 90% CIs for RD and RR were within the bioequivalence margin of -13% to 13% for RD and 0.759 to 1.318 for RR. Secondary endpoints included safety.

Results: Of the 827 enrolled patients, 725 were randomized (ABP 980: n = 364; TRAS: n = 361); 696 (ABP 980: n = 358; TRAS: n = 338) were included in the pCR evaluable population. Based on local review, 48.0% and 40.5% of patients in the ABP 980 arm and TRAS arm, respectively, achieved pCR. RD and RR of pCR were 7.3% (90% CI: 1.2%, 13.4%) and 1.19 (90% CI: 1.033, 1.366), with the upper bound CI slightly exceeding the equivalence margin. Based on central independent review, 47.8% and 41.8% in the ABP 980 arm and TRAS arm achieved pCR. RD and RR of pCR were 5.8% (90% CI: -0.5, 12.0%) and 1.14 (90% CI: 0.993, 1.312), contained within the equivalence margin. 292 (80.2%) and 287 (79.5%) in the ABP 980 and TRAS arm, respectively, had ≥1 adverse event (AE); 54 (14.8%) patients in the ABP 980 arm and 51 (14.1%) in the TRAS arm had a Grade ≥3 AE. Most common AEs (ABP 980 vs TRAS) were arthralgia (17.3% vs 15.2%), asthenia (14.8% vs 16.3%), neutropenia (14.6% vs 12.5%), peripheral neuropathy (13.7% vs 11.9%), and anemia (11.0% vs 10.2%).

Conclusions: Results of this study show clinical equivalence of ABP 980 and TRAS in the neoadjuvant setting and add to the totality of evidence demonstrating similarity between ABP 980 and TRAS.

Clinical trial identification: 20120283

Legal entity responsible for the study: Amgen Inc.

Funding: Amgen Inc.

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152PD Double-blind, randomized phase III study to compare the efficacy and safety of trastuzumab and its biosimilar candidate CT-P6 in HER2 positive early breast cancer (EBC)

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Background: CT-P6 is a proposed biosimilar to Reference Trastuzumab (RTZ). This trial (2013-004525-84) evaluated the similarity of CT-P6 and RTZ in efficacy and safety for HER2+ EBC.

Methods: 549 patients with HER2+ EBC were randomized to receive CT-P6 (n = 271) or RTZ (n = 278) in combination with docetaxel (Cycles 1-4) and 5-fluorouracil, epirubicin and cyclophosphamide (Cycles 5-8). CT-P6 or RTZ was administered at 8 mg/kg (Cycle 1 only) followed by 6 mg/kg every 3 weeks. After surgery, patients received CT-P6 or RTZ monotherapy up to 10 cycles. The primary endpoint was pathological complete response (pCR) rate at surgery. Secondary endpoints were overall response rate (ORR), PK, PD and safety.

Results: The pCR rate was 46.8% in CT-P6 and 50.4% in RTZ. The 95% CIs for the estimate of treatment difference were within the equivalence margin (±0.15) in both PPS and ITT. The proportion of patients with at least 1 SAE was 7.4% in CT-P6 and 11.9% in RTZ over 1-year treatment. 6 patients (3 in CT-P6 and 3 in RTZ) withdrew treatment due to significant LVEF decrease. Infusion related reaction was reported for 11.4% of patients in CT-P6 and 10.4% of patients in RTZ.

Table: 152PD Summary of efficacy endpoints

	PPS		ITT	
	CT-P6 n = 248	RTZ n = 256	CT-P6 n = 271	RTZ n = 278
pCR (ypT0/is ypN0)				
pCR rate	46.8	50.4	43.5	47.1
(95% CI)	(40.4 – 53.2)	(44.1 – 56.7)	(37.6 – 49.7)	(41.1 – 53.2)
Difference estimate	−0.0362		−0.0358	
(95% CI)	(−0.1238 – 0.0516)		(−0.1198 – 0.0480)	
pCR (ypT0 ypN0)				
pCR rate	39.9	41.4	37.3	38.8
(95% CI)	(33.8 – 46.3)	(35.3 – 47.7)	(31.5 – 43.3)	(33.1 – 44.9)
Difference estimate	−0.0149		−0.0158	
(95% CI)	(−0.1022 – 0.0731)		(−0.0996 – 0.0685)	
ORR (independent review)				
ORR	88.3	89.5	86.3	87.1
(95% CI)	(83.6 – 92.0)	(85.0 – 92.9)	(81.7 – 90.2)	(82.5 – 90.8)
Difference estimate	−0.0115		−0.0070	
(95% CI)	(−0.0990 – 0.0764)		(−0.0911 – 0.0769)	

Conclusions: This study demonstrated the equivalence of efficacy between CT-P6 and Reference Trastuzumab in EBC patients. Secondary efficacy endpoints also supported the similarity for two study drugs. CT-P6 was well tolerated with a similar safety profile to that of Reference Trastuzumab through the neoadjuvant and adjuvant period.

Clinical trial identification: EudraCT Number: 2013-004525-84 NCT Number: NCT02162667

Legal entity responsible for the study: Celltrion, Inc.

Funding: Celltrion, Inc.

Disclosure: F.J. Esteva: Consulting Role: Celltrion, Inc. G. Dzagnidze: Research funding: Celltrion, Inc., Roche, AstraZeneca Pharmaceutical, Inc. A. Eniu: Research Funding: Roche, AstraZeneca, Celltrion, Inc., Pfizer. Travel, Accommodations, Expenses: Roche, AstraZeneca, Teva. G. Morar-Bolba: Consulting or Advisory Role: Pierre Fabre. Travel, Accodomations, Expenses: Roche. R.K. Li: Research Funding: Pfizer, GlaxoSmithKline, AstraZeneca, Novartis, Celltrion, Inc. S.J. Lee: Employment, Board of Directions, Stock ownership, Travel, Accommodations, Expenses: Celltrion, Inc. S. Yu: Employment, Stock ownership, Travel, Accommodations, Expenses: Celltrion, Inc. J. Stebbing: Consulting or Advisory Role: Celltrion, Inc. All other authors have declared no conflicts of interest.

153PD One-year safety, immunogenicity, and survival results from a phase III study comparing SB3 (a proposed trastuzumab biosimilar) and originator trastuzumab in HER2-positive early breast cancer treated with neoadjuvant-adjuvant treatment

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Background: Equivalence for efficacy between SB3 (a proposed trastuzumab biosimilar) and originator trastuzumab (TRZ) in terms of breast pathologic complete response (bpCR) rates has been demonstrated and previously reported.[1] Here we present the one-year results on safety, immunogenicity, event-free-survival (EFS), and overall survival (OS).

Methods: Study compared neoadjuvant SB3 or TRZ for 8 cycles concurrently with chemotherapy (4 cycles of docetaxel followed by 4 cycles of 5-fluorouracil/epirubicin/cyclophosphamide). Patients then underwent surgery followed by 10 cycles of adjuvant SB3 or TRZ as randomised. The primary endpoint was bpCR rate and secondary endpoints included safety, immunogenicity, EFS, and OS up to the adjuvant period.

Results: A total of 875 patients were randomised with a median follow-up duration of 438 days, and 765 patients completed adjuvant therapy (SB3, N = 381; TRZ, N = 384). Incidences of treatment emergent adverse events (TEAEs) were comparable between arms (Table). Most frequently occurring TEAEs were alopecia, neutropenia, and nausea during the neoadjuvant period and radiation skin injury, procedural pain, and fatigue during the adjuvant period. EFS rates were 92.2% in SB3 and 91.6% in TRZ (hazard ratio 0.94; 95% CI, 0.59 to 1.51). There were a total of 6 deaths (SB3, N = 1; TRZ, N = 5). Immunogenicity was low and comparable, with anti-drug antibody positive for 3 patients (0.7%), in each arm.

Table: 153PD Safety profile

	SB3 N = 437 n, (%)	TRZ N = 438 n, (%)
Incidence of TEAEs	426 (97.5)	421 (96.1)
Grade ≥ 3 TEAEs	325 (74.3)	315 (71.9)
TEAEs of special interest*	48 (11.0)	53 (12.1)
Serious TEAEs	56 (12.8)	58 (13.2)
Death	1 (0.2)	5 (1.1)

*Includes infusion-related reaction, left ventricular systolic dysfunction, and congestive heart failure.

Conclusions: One-year safety, immunogenicity, and survival results further support the biosimilarity established between SB3 and TRZ. Reference: 1. Pivot X et al. ASCO 2017, ID509.

Clinical trial identification: EudraCT Number: 2013-004172-35 ClinicalTrials.gov NCT02149524

Legal entity responsible for the study: Samsung Bioepis Co., Ltd.

Funding: Samsung Bioepis Co., Ltd.

Disclosure: X. Pivot: Consultant with honorarium for Samsung Bioepis Co., Ltd. L. Younju, J. Lim: Employee of Samsung Bioepis Co., Ltd. Stock ownership of Samsung Biologics. All other authors have declared no conflicts of interest.

154PD A randomized, double-blind study of PF-05280014 (a potential biosimilar) vs trastuzumab, both given with docetaxel (D) and carboplatin (C), as neoadjuvant treatment for operable human epidermal growth factor receptor 2-positive (HER2+) breast cancer

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Background: This comparative clinical trial evaluated efficacy, safety, immunogenicity and pharmacokinetics (PK) of PF-05280014, a potential trastuzumab biosimilar, vs trastuzumab sourced from the EU (trastuzumab-EU), both given with D and C, as neoadjuvant treatment for operable HER2+ breast cancer.

Methods: Patients (pts; N = 226) were stratified by primary tumor size and hormone receptor status and randomized 1:1 to receive PF-05280014 or trastuzumab-EU (8 mg/kg at Cycle 1; 6 mg/kg thereafter), both with D (75 mg/m^2) and C (target AUC 6), every 3 wks for 6 treatment cycles. The study was powered to test whether PF-05280014 was noninferior to trastuzumab-EU in the percentage of pts with Cycle 5 C_{trough} (pre-dose Cycle 6) >20 µg/mL. Efficacy was measured by the percentage of pts with pathological complete response (pCR), defined as the absence of invasive neoplastic cells in breast and lymph nodes after neoadjuvant therapy, and objective response rate (ORR). Safety and immunogenicity were also assessed.

Results: The percentage of pts with Cycle 5 C_{trough} >20 µg/mL was 92.1% for PF-05280014 and 93.3% for trastuzumab-EU; the lower limit of the 95% CI (-8.02% to 6.49%) for the stratified difference between groups was above the noninferiority margin (-12.5%). The pCR rate was 47.0% (95% CI: 36.9-57.2) for PF-05280014 and 50.0% (95% CI: 39.0-61.0) for trastuzumab-EU. Central radiology review-assessed ORR was 88.1% (95% CI: 80.2-93.7) for PF-05280014 and 82.0% (95% CI: 72.5-89.4) for trastuzumab-EU. All causality, grade 3-4 treatment-emergent adverse events were reported by 38.1% (PF-05280014) vs 45.5% (trastuzumab-EU) of pts. No pts in the PF-05280014 and 1 (0.89%) in the trastuzumab-EU group had positive anti-drug antibody titer.

Conclusions: PF-05280014 demonstrated similarity in efficacy, safety and immunogenicity, and noninferiority in PK to trastuzumab-EU. A separate comparative safety and efficacy study (NCT01989676) is evaluating PF-05280014 vs trastuzumab-EU, both given with paclitaxel, as first-line treatment for HER2+ metastatic breast cancer.

Clinical trial identification: NCT02187744; EudraCT No: 2013-004679-11

Legal entity responsible for the study: Pfizer Inc.

Funding: Pfizer Inc.

Disclosure: P.E. Lammers: Advisory boards with Pfizer Inc. M. Dank: Member of Biosimilars Oncology European Advisory Board with Pfizer Inc since 2013. R. Abbas, F. Hilton, J. Coiro, I. Jacobs: Full time employee and lares stock holdings and/or stock options from Pfizer Inc. All other authors have declared no conflicts of interest.

155PD Tumor-infiltrating lymphocytes (TILs) in HER2-positive (HER2+) early breast cancer treated with neoadjuvant lapatinib and trastuzumab without chemotherapy in the PAMELA Trial

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Background: Increased number of TILs at baseline is associated with pathological complete response (pCR) and improved outcomes in HER2+ early breast cancer (BC) treated with anti-HER2-based chemotherapy. The associations in the neoadjuvant setting in the absence of chemotherapy and the effect of on-treatment TILs changes on pCR in the breast (pCR_B) are unknown.

Methods: PAMELA is a prospective study in HER2+ BC designed to evaluate the ability of the PAM50 intrinsic subtypes (IS) to predict pCR_B following neoadjuvant lapatinib and trastuzumab (with hormonal therapy if hormone receptor-positive[HR+]). Levels of TILs as continuous and categorical (TILs-low = <50%, TILs-high = >50%) variables and their changes were correlated with pCR_B.

Results: TILs evaluation was available for 148 baseline (BS) and 134 Day-15 (D15) samples of 151 recruited patients. At BS, the median (interquartile range) levels of TILs were 10% (5-20). Median TILs distribution according to IS was: HER2-E (10%), Luminal (Lum) A (7.5%), LumB (5%), Basal-like (5%) ($p = 0.02$). Levels of TILs were higher in HR- (10%, 1-20) vs HR + (5%, 1-20) tumors, although not statistically significant ($p = 0.07$). pCR_B rates were 58.3% (7/12) for TILs-high and 27.2% (37/136) for TILs-low ($p = 0.03$). At baseline, TILs were significantly associated with pCR in univariate analysis. At D15, median levels of TILs were 15% (5-30) with an increase across all the different IS ($p < 0.01$). The distribution across IS at D15 was: HER2-E (20%), Lum A (10%), Lum B (7.5%), Basal-like (20%) and Normal-Like (10%) ($p = 0.37$). At D15, TILs-high tumors showed a pCR_B rate of 65% (13/20) vs 21.1% (24/114) of TILs-low ($p < 0.01$). As a continuous variable, higher TILs levels at D15 and changes of TILs levels from BS to D15 were associated with higher pCR_B rates independently of HR status and IS ($p < 0.01$). When analysis was performed for HR-negative and HR-positive patients, separately in both cohorts, TILs at D15 was significantly associated with pCR.

Conclusions: The presence of TILs at D15 is an independent predictive marker of pCR_B in HER2+ early BC treated with neoadjuvant anti-HER2 agents without chemotherapy.

Clinical trial identification: NCT01973660

Legal entity responsible for the study: SOLTI Breast Cancer Research Group

Funding: GlaxoSmithKline (now Novartis)

Disclosure: All authors have declared no conflicts of interest.

156PD Targeted NGS profiling identifies genomic alterations associated with high-risk eBC

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Background: Identifying early breast cancer (eBC) patients that require adjuvant chemotherapy is defined by clinical features, which do not accurately identify high-risk patients. The USO01062 Phase 3 study enrolled 2,611 high-risk patients based on clinical features, with a 13% event rate observed. Comparing the genomic landscape of tumors between patients who had a recurrence event and those who did not may uncover genomic aberrations associated with recurrence that may be used to identify high-risk patients. The genomic landscape of TNBC subtypes is also largely unknown and NGS profiling may shed light on novel therapeutic opportunities.

Methods: The USO01062 study failed to show a benefit for the addition of capecitabine to adjuvant chemotherapy (O'Shaughnessy J. *et al.* 2015). Arms were pooled and DNA and RNA were extracted from 1,181 tumor samples, of which 145 patients had a DFS event, and were matched demographically to a set of 146 patients without an event for targeted NGS profiling using FoundationOne®. Gene expression was previously run using a breast cancer specific 800-gene panel (Wilson T.R. *et al.* 2016).

Results: Analysis of somatic alterations within IHC subtypes identified unique prognostic factors, e.g. alterations in *ATM*, *ERCC4* and *IGF2R* correlated with a worse HR in HR+ disease, whereas alterations in *MAP3K1*, *RPTOR* and *LYN* correlated with a worse HR in TNBC. Analysis of tumor mutational burden (TMB) revealed TNBC tumors had the highest burden, which did not correlate with clinical outcome or expression of *PDL1* and *CD8* genes. Molecular subtyping of TNBC (Lehmann B.D. *et al.* 2011) found distinct genetic drivers in each subtype, e.g. alterations in *TP53* and *MYC* were the most frequent in BL1 and BL2 tumors. IM tumors expressed alterations in *TP53*, *CREBBP* and *BRCA1*. LAR tumors expressed alterations in *PIK3CA* and *PTEN*.

Conclusions: TMB was not prognostic and did not correlate with *PDL1* or *CD8* gene expression, suggesting that TMB in TNBC may not be a surrogate for the immune activated subtype. TNBC molecular subtyping identified different genomic drivers providing evidence for genomic heterogeneity within subtypes. Lastly, comparison of patients that experienced a DFS event identified genomic alterations that may be used to identify high-risk patients.

Clinical trial identification: Patients were enrolled onto the parent study USO01062, (NCT00089479).

Legal entity responsible for the study: Hoffmann-La Roche

Funding: Genentech, Inc.

Disclosure: T.R. Wilson, A.R. Udyavar, C-W. Chang, J. Giltnane, J.M. Spoerke, J. Aimi, H. Savage, A. Daemen, R. Bourgon, M.R. Lackner: Employed by Genentech, Inc. Stocks in Roche

157PD 10 years follow up of the RASTER study; implementing a genomic signature in daily practice

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Background: In 2004 the 70-gene signature, MammaPrint® (MP), developed to predict High or Low Risk of distant breast cancer (BC) recurrence, was introduced in the observational RASTER trial. Patients (cT1–3N0M0) and their doctors took the clinical Dutch guideline and MP in to account to decide on adjuvant systemic treatment (AST). Five years follow-up data confirmed the prognostic value of the MP (Drukker, Int J Cancer, 2013). In this analysis we report the outcome at 10 years.

Methods: Ten year survival data was available for all 427 Raster patients, age < 61. For the current analysis, clinical high (C-high) or low (C-low) risk was scored according to the modified version of Adjuvant! Online (Cardoso, N Engl J Med, 2016). 10-year distant-recurrence-free-interval (DRFI) probabilities were compared between risk groups based on the 70-gene signature and clinical assessment.

Results: The 70-gene signature identified 51.4% (219/427) patients with a genomic Low Risk of BC recurrence (G-low). 10-year DRFI in patients with G-low or genomic High Risk (G-high) was 93.7% and 86.8% respectively (HR 1.4; 95% confidence interval{CI] 1.0-1.9). Clinical assessment identified 57% as C-low. The 10-year DRFI was 91.7% in C-low and 88.2% in C-high (HR 1.4; 95%CI 0.8-2.6). The 10-year DRFI in the combined genomic and clinical riskgroups was 94.4% in patients with a C-low/G-Low profile, only 11.6% of them received AST. In the C-low/G-High group 10-years DRFI was 88.5%, over 90% of them received AST. For C-high risk patients 10-year DRFI was 90.9% if G-Low (n = 46) and 87.3% if G-High (n = 137). In ER-positive BC (ER+) (N = 342) 10-years DRFI was 93.6% (G-Low) versus 88.8% (G-High) (HR 1.6; 95%CI 0.8-3.3). With clinical risk assessment, 10-years DRFI in ER+ was 91.6% (C-low) versus 91.9% (C-high).

Conclusions: Patients who omitted chemotherapy based on MammaPrint Low Risk had an excellent 10 year DRFI, confirming the prognostic value of the MP. When C-high, the MP identified another 10.8% (46/426) of patients as G-Low who might forego adjuvant chemotherapy if ER+. In contrast to genomic risk stratification, the clinical risk assessment was unable to differentiate for survival between ER+ C-high and C-low risk patients.

Legal entity responsible for the study: S. Linn

Funding: None

Disclosure: All authors have declared no conflicts of interest.

158PD Adjuvant anti-HER2 therapy, treatment-induced amenorrhea (TIA) and survival in premenopausal patients (pts) with HER2-positive (HER2+) early breast cancer (EBC): Analysis from the ALTTO trial (BIG 2-06)

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Background: In premenopausal pts with HER2+ EBC, the prognostic effect of TIA is unknown and the gonadotoxicity of trastuzumab (T) and lapatinib (L) remains largely uncertain. We aimed to assess the prognostic effect of TIA and the impact of T and/or L on the risk of developing TIA in premenopausal pts with HER2+ EBC.

Methods: ALTTO was an international, open-label, randomised phase 3 trial in pts with HER2+ EBC. Pts were randomised in 4 adjuvant anti-HER2 arms: T alone, L alone, a sequence of the 2 agents (T->L) and their combination (T+L). As per study protocol, menopausal status was collected in all pts at randomisation and at week 37. By selecting only premenopausal pts at randomisation, we investigated whether TIA in pts with hormone receptor-positive (HR+) and negative (HR-) EBC would impact on disease-free (DFS) and overall survival (OS), and the risk factors for developing TIA. Landmark and time-dependent modeling were used to account for guaranteed time bias.

Results: Out of 8381 pts randomised in ALTTO, 2862 were included in this analysis. Median age was 43 years (range 38-47); 1679 (59%) pts had HR+ EBC. Pts with HR+/HER2+ EBC who experienced TIA had significant better DFS (hazard ratio [HR] 0.64; 95% confidence intervals [CI] 0.52-0.79) and OS (HR 0.53; 95% CI 0.38-0.74) than those who did not have TIA. By contrast, pts with HR-/HER2+ EBC had similar DFS (HR 0.85; 95% CI 0.68-1.07) and OS (HR 0.89; 95% CI 0.64-1.25) regardless of whether they had TIA (interaction P for DFS=0.009 and for OS = 0.002). A similar TIA rate was observed in the T (72.6%), L (74.0%), T->L (72.1%) and 74.8% (T+L) arms ($p = 0.644$). Older age ($p < 0.001$), addition of taxanes to anthracycline-based chemotherapy ($p < 0.001$), and use of adjuvant endocrine therapy ($p < 0.001$) significantly increased the risk of TIA.

Conclusions: In premenopausal pts with HR+/HER2+ EBC, TIA was associated with significant survival benefits. Anti-HER2 agents did not impact the likelihood of developing TIA. These data are of great importance in oncofertility counseling and support the use of ovarian suppression as part of adjuvant endocrine therapy in premenopausal HR+/HER2+ EBC pts.

Clinical trial identification: The trial is registered with the clinicaltrial.gov identifier, number NCT00490139.

Legal entity responsible for the study: Novartis Pharma AG, Basel, Switzerland

Funding: Novartis Pharma AG and the National Cancer Institut of the National Institutes of Health.

Disclosure: E. De Azambuja: Honoraria from Roche. Travel grants from Roche and GlaxoSmithKline outside the submitted work.

All other authors have declared no conflicts of interest.

159PD Neoadjuvant therapy with trastuzumab emtansine and pertuzumab in patients with HER2-positive primary breast cancer (A randomized, phase 2 study; JBCRG-20)

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Background: Exploration of neoadjuvant chemotherapy with anti-HER2 therapy to achieve higher pathological complete response (pCR) is important. We focused on trastuzumab emtansine (T-DM1), pertuzumab (P) and tailored response guided therapy in HER2+ primary breast cancer (cT1c–T3, cN0–N1, M0, tumor ≤ 7 cm).

Methods: This randomized phase II study evaluated efficacy and safety of 3 regimens, A) 6 cycles TCbHP, B) 4 cycles TCbHP followed by 4 cycles T-DM1+P, and C) 6 cycles T-DM1+P: responders to 4 cycles T-DM1+P were assigned to 2 more cycles [C1] or non-responders were assigned to 4 cycles FEC [C2] (Table). Responders: $\geq$30% decrease in tumor size (MRI) and Ki67 $\leq$10% or no cancer cells in core needle biopsy. ER(+) patients received anti-hormonal therapy concurrent to T-DM1+P. HER2, ER and Ki-67 were assessed in a central laboratory. Primary endpoint was pCR rate (yT0-is, yN0; centrally confirmed). Secondary endpoints were safety, ORR and breast conservation rate.

Results: A total of 206 patients were enrolled (Aug 2014-Feb 2016; full analysis set, n = 204). Patient characteristics were comparable among all groups (median age 53.0 y,

Table: 159PD Summary of response

Variable	Group A (6-cycle TCbHP) % (n = 51)	Group B (4-cycle TCbHP switched to 4-cycle T-DM1+P) % (n = 52)	Group C1 (4-cycle T-DM1+P continued 2-cycle T-DM1+P) % (n = 80)	Group C2 (4-cycle T-DM1+P switched to 4-cycle FEC) % (n = 21)	Group C % (n = 101)
pCR rate, Overall	56.9 (29/51)	71.2 (37/52)	62.5 (50/80)	38.1 (8/21)	57.4 (58/101)
pCR rate, ER (-)	76.2 (16/21)	73.9 (17/23)	72.2 (26/36)	33.3 (2/6)	66.7 (28/42)
pCR rate, ER (+)	43.3 (13/30)	69.0 (20/29)	54.5 (24/44)	40.0 (6/15)	50.8 (30/59)
ORR	96.1 (49/51)	86.5 (45/52)	88.8 (71/80)	85.7 (18/21)	88.1 (89/101)
cCR	47.1 (24/51)	51.9 (27/52)	38.8 (31/80)	38.1 (8/21)	38.6 (39/101)
Breast conservation rate	52.0 (26/50)	51.9 (27/52)	54.4 (43/79)	38.1 (8/21)	51.0 (51/100)
Breast conservation rate from planned mastectomy	34.4 (11/32)	38.7 (12/31)	36.7 (18/49)	14.3 (2/14)	31.7 (20/63)

Dose was administered every 3 weeks as adjuvant therapy. ER (+) patients received concurrent endocrine therapy during T-DM1 treatment. ER, estrogen receptor; FEC, 5-fluorouracil/epirubicin/cyclophosphamide; ORR, overall response rate; pCR, pathological complete response; TCbHP, docetaxel/carboplatin/trastuzumab + pertuzumab; T-DM1+P, trastuzumab emtansine + pertuzumab

post-menopause 53.9%, T2 70.6%, median tumor size 26 mm, N0 63.2%, ER(+) 57.8%). In group C, 80 (79.2%) patients continued T-DM1+P due to favorable response. pCR rate in group A, B, and C was 56.9%, 71.2%, and 57.4%. By exploratory analyses, pCR rate was higher for groups B and C1 than A in ER(+), but comparable in ER(-) patients. No significant differences in secondary endpoints. No treatment discontinuation due to AEs and similar drug-related SAE profile were seen among groups. Of specific mention: low drug-related alopecia in group C1 (5.0%) than A, B or C2 (81%–94%) and less febrile neutropenia in C1 (0%) than A, B or C2 (15%–33%).

Conclusions: Addition of T-DM1+P to standard TCbHP regimen may be possibly superior to TCbHP. Tailored T-DM1+P is a promising approach with mostly equal efficacy and less toxicity compared to TCbHP.

Clinical trial identification: UMIN-CTR: UMIN000014649

Legal entity responsible for the study: Japan Breast Cancer Research Group

Funding: Japan Breast Cancer Research Group and Chugai Pharmaceutical Co., Ltd.

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160PD Statistical model to predict brain metastasis risk in patients with early-stage breast cancer

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Background: Breast cancer (BC) brain metastases (BCBM) are emerging as a major factor of morbidity and poor overall survival. We hypothesized that a clinical risk prediction model could predict BCBM and allow the selection of an enriched early-stage BC patient population, who are at higher risk for BCBM, for preventive trials.

Methods: Electronic medical records were retrospectively reviewed for patients diagnosed and treated for early-stage BC at MD Anderson Cancer Center between 1997 and 2014 under a study approved by the institutional review board. The clinicopathologic prognostic features selected for analysis are: age, HER-2 receptor status and hormone receptor (HR) status, tumor histology, grade, and stage, menopausal status, vascular and lymphatic invasion. A multivariate Cox proportional hazards regression analysis was conducted.

Results: A total of 15164 patients with complete data for key variables were studied. Patients were randomly split 2:1 into training and validation sets. Of the 10026 patients in the training set, 317 developed BCBM and of the 5138 in the validation set, 133 developed BCBM. The 10-year estimated risk of brain metastasis was 4.2% (95% CI, 3.7% to 4.7%) in the training set. Younger age, HER-2 negative and HR-negative receptor status, higher tumor stage and grade, were all significantly and independently associated with BCBM. The risk prediction model had an estimated Harrell's concordance index of 81% (95%CI, 77% to 86%) in the validation set. In the 10% of validation set patients predicted to have the highest risk, the 10-year risk of brain metastasis was 15% (95% CI, 11% to 18%).

Conclusions: This risk prediction model for brain metastasis risk in early BC allows us to: (1) Identify the significant clinical risk factors for BCBM, (2) use these risk factors to develop an individualized risk score for BCBM, and (3) use this score to select patients at higher risk of BCBM to be prioritized for preventive trials.

Legal entity responsible for the study: Nuhad K. Ibrahim

Funding: Sheril Wynne Research Fund.

Disclosure: All authors have declared no conflicts of interest.

161PD Surrogate endpoints for overall survival in randomized controlled trials evaluating adjuvant treatment for breast cancer: A meta-analysis

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Background: In cancer randomized controlled trials (RCT), endpoints other than overall survival (OS) such as disease-free survival (DFS) are increasingly being used as primary endpoint. Their development is influenced by the need to reduce the number of patients, the duration and ultimately the cost of the trials. Their use as primary endpoint however require a rigorous validation as surrogate endpoints for OS. In adjuvant breast cancer, only a few studies evaluated surrogate endpoints for OS, limited by the use of aggregate data. We present the results of a meta-analysis of individual-patient data assessing surrogate endpoints for OS in the context of adjuvant breast cancer.

Methods: We evaluated four endpoints as potential surrogates for OS relying on a meta-analysis of 5 phase III trials: relapse-free survival (RFS), invasive DFS, locoregional RFS and distant DFS. At the patient level, we estimated the individual-level associations by jointly modeling each surrogate with OS using a copula function. At the trial level, we estimated the association between the treatment effects using (1) a linear regression model weighted by the trial size and (2) the two-step model proposed by Burzykowski, Molenbergh and Buyse.

Results: We gathered individual-patient data from 11676 patients from 5 RCT. The endpoints were highly associated with OS at the patient level ($r \geq 0.98$). At the trial level, invasive DFS showed the higher association with OS (R^2_{WLR}=0,78; R^2_{2SM}=0,87).

Conclusions: This is the first meta-analysis on individual-patient data evaluating surrogate endpoints for OS in adjuvant breast cancer. These results suggest that the endpoints could be interesting candidate surrogates for OS, but further evaluation on a larger set of trials is required to improve the precision of our estimations of the trial-level associations.

Legal entity responsible for the study: ICM Regional Cancer Center of Montpellier

Funding: French National Insitute of Cancer (INCa)

Disclosure: All authors have declared no conflicts of interest.

162PD Pathological response in a triple-negative breast cancer cohort treated with neoadjuvant carboplatin and docetaxel according to Lehmann's refined classification (TNBCtype-4)

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Background: Triple-negative breast cancer (TNBC) is an aggressive subtype of BC in need for predictive biomarkers of response to neoadjuvant chemotherapy (NACT). We aimed to evaluate the predictive value of the TNBCtype-4 classifier in a population of TNBC treated with carboplatin and docetaxel (TCb).

Methods: Patients with stage I-III TNBC (ER and PR < 1%, HER2-negative) were accrued in a non-randomized trial of neoadjuvant carboplatin AUC 6 and docetaxel 75 mg/m2 q3 weeks (NCT01560663). Pathological complete response (pCR) was defined as the absence of invasive tumor in the breast and axillary lymph nodes (ypT0/is ypN0) and residual disease was evaluated using the residual cancer burden (RCB) method (Symmans et al 2007). RNAseq was performed from FFPE-extracted mRNA from the basal core biopsy, and RNAseq data was uploaded into the TNBCtype online tool (http://cbc.mc.vanderbilt.edu/tnbc). Correlation studies were analyzed with R studio v 3.2.1.

Results: RNAseq was available for 94 of the 121 patients enrolled. Patients included had a median age at diagnosis of 51 years (range 28-78), 69.1% had nodal involvement and 52.1% and 46.8% had stage II and III disease, respectively. pCR rate and pathological good response (pCR or RCBI) were 44.7% and 56.4%. TNBCtype-4 distribution was: 34.0% BL1, 20.2% BL2, 23.4% M and 14.9% LAR. An additional 7.4% were classified as ER-positive. BL1 was associated with a significant younger age at diagnosis and higher ki67 values. TNBCtype-4 showed a significant association with response to NACT ($p = 0.027$), even in multivariate analysis including tumor size and nodal status, with BL1 patients achieving the highest pCR rate (65.6%), followed by BL2 (47.4%). Conversely, LAR and ER-positive showed the lowest pCR rates, 21.4% and 14.3%. When compared to BL1, LAR and M subtypes had an OR of achieving a pCR of 0.14 and 0.30 respectively ($p < 0.05$).

Conclusions: TNBCtype-4 shows a significant predictive value of response in a TNBC cohort homogeneously treated with TCb, with BL1 and LAR displaying the best and worse responses to NACT respectively.

Clinical trial identification: NCT01560663

Legal entity responsible for the study: Hospital General Universitario Gregorio Marañon

Funding: Institute of Health Carlos III (PI12-02684)

Disclosure: All authors have declared no conflicts of interest.

163PD Long-term survival analysis of the randomized phase II trial investigating the addition of carboplatin to neoadjuvant therapy for triple-negative (TNBC) and HER2-positive early breast cancer (GeparSixto)

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Background: Patients (pts) with TNBC involved in the GeparSixto study showed an improved pCR rate (ypT0 ypN0) with the addition of carboplatin (Cb) to anthracycline/taxane-based neoadjuvant chemotherapy, which translated in an improved early disease-free survival (DFS). No difference was observed in the HER2+ subgroup for pCR and DFS by adding Cb. Here, we present the results on the long-term survival analysis.

Methods: In the GeparSixto trial, pts were treated for 18 weeks with paclitaxel 80mg/m^2 q1w and non-pegylated-liposomal doxorubicin (NPLD) 20mg/m^2 q1w (PM), concurrently with bevacizumab 15mg/kg q3w if TNBC or trastuzumab 6(8)mg/kg q3w and lapatinib 750mg daily if HER2+. 595 pts were randomised 1:1 to receive concurrently Cb AUC 1.5-2.0 q1w (reduced to 1.5 by an amendment after 330 pts) vs no Cb, stratified by subtype (HER+ vs TNBC), 588 pts started treatment. Primary objective was pCR (ypT0 ypN0). DFS, distant (DDFS), loco regional recurrence-free (LRRFS) and overall survival (OS) were secondary objectives.

Results: After a median follow-up of 47.3 months (range 1.7-62.8) overall no significant difference in DFS was seen with PMCb vs PM (HR = 0.83 [95%CI 0.58-1.20]; p = 0.327). However, Pts with TNBC had a significantly better DFS (HR = 0.56 [95%CI 0.34-0.93]; p = 0.024) and DDFS (HR = 0.50 [95%CI 0.29-0.86]; p = 0.013) when treated with PMCb. No difference was seen in pts with HER2+ disease (DFS HR = 1.34 [95%CI 0.77-2.34]; p = 0.295; interaction test p = 0.022 and DDFS HR = 1.56 [95% CI 0.86-2.83]; p = 0.145; interaction test p = 0.006). A trend towards a better OS was observed in pts with TNBC (HR = 0.60 [95%CI 0.32-1.12]; p = 0.110). OS was not different between the two arms, neither overall (HR = 0.72 [95%CI 0.43-1.21]; p = 0.223) nor in HER2+ disease (HR = 1.13 [95%CI 0.44-2.93]; p = 0.800). Multivariable analysis comfirms that pCR (pCR vs no pCR) independently predicted DFS (HR = 0.23, p < 0.001), DDFS (HR = 0.21, p < 0.001), and OS (HR = 0.29, p = 0.002).

Conclusions: Long-term survival analysis supports the neoadjuvant use of Cb in TNBC. The value of pCR as a strong predictor of DFS and OS was confirmed.

Clinical trial identification: NCT 01426880

Legal entity responsible for the study: German Breast Group

Funding: Teva, GSK, Roche, Hexal

Disclosure: G. von Minckwitz, S. Loibl: Research grant to the institution from Teva. All other authors have declared no conflicts of interest.

164P Impact of lack of surgery on outcomes in elderly patients with non-metastatic breast cancer (BC): A population based study using the SEER 18 data base

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Background: Elderly women with non-metastatic BC do not always receive standard of care definitive surgical treatment. Both provider and patient related reasons have been cited. The impact of omitting surgery in elderly patients who otherwise would be candidates for surgery has not been addressed. We performed a population based study to evaluate the impact of lack of surgery on survival outcomes in elderly women with BC in modern era.

Methods: The Surveillance, Epidemiology and End Results database was queried from 2010 to 2013 for female patients age 60 and older with a diagnosis of invasive ductal or lobular BC with AJCC stage I, II, III. To determine the relationship between surgery at diagnosis and survival and to take into consideration the effect of comorbidities, we organized patients in the following groups: a. Surgery performed, b. Surgery recommended, but not performed; c. Surgery not recommended and not performed. The Kaplan –Meier method was used to generate survival curves and the log-rank test was performed to compare OS rates among different groups.

Results: 119,404 patients were eligible with a median age between 70 to 74 years old. 71,638 (60%) patients were stage I, 37,524 (31.42%) were stage II and 10,245 (8.58%) were stage III. 85.2% were ER +, 12.4% were Her 2 + and 8.8% were triple negative (TN). Compared with the patients who received surgery, patients who did not receive surgery had a significantly worse outcome (all patients: HR = 7.39, 95% CI, 6.98–7.83, P < 0.001. Patients who were recommended to have surgery but did not receive it had significantly inferior survival than patients who underwent surgery (HR = 5.08, 95% CI, 4.48–5.76, P < 0.001) although better OS than those who were recommended against surgery (HR = 0.62, 95% CI, 0.54–0.71, P < 0.001). Similar results were found in subgroup analyses regardless of age, tumor stage, ER or HER2 status. Patients with TNBC who did not received surgery also had a significantly worse OS than those who received surgery. (HR = 4.89, 95% CI, 4.07–5.88, P < 0.001).

Conclusions: Definitive surgery should be performed in medically-fit elderly patients with non-metastatic BC due to a significant survival benefit.

Legal entity responsible for the study: Cristina Truica

Funding: None

Disclosure: All authors have declared no conflicts of interest.

166P Eight-year follow up results of the OTOASOR trial: The optimal treatment of the axilla – surgery or radiotherapy after positive sentinel lymph node biopsy in early-stage breast cancer. A randomized, single centre, phase III, non-inferiority trial

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Background: The National Institute of Oncology, Budapest conducted a single centre randomized clinical study. The OTOASOR (Optimal Treatment Of the Axilla – Surgery Or Radiotherapy) trial compares completion of axillary lymph node dissection (cALND) to regional nodal irradiation (RNI) in patients with sentinel lymph node metastasis (pN1sn) in stage I-II breast cancer.

Methods: Patients with primary invasive breast cancer (cN0 and cT $\leq$ 3cm) were randomized before surgery for cALND (standard treatment) or RNI (investigational treatment). Sentinel lymph nodes (SN) were investigated with serial sectioning at 0.5 mm levels by haematoxylin-eosin staining. Investigational treatment arm patients received 50Gy RNI instead of cALND. Adjuvant treatment and follow up were performed according to the actual guidelines. Between August 2002 and June 2009, 1,054 patients were randomized for cALND and 1052 patients for RNI. SN was evaluated in 2,073 patients and was positive in 526 patients (25.4%). 474 cases were evaluable (244 in the cALND and 230 in the RNI arm), and in the cALND group 94 of 244 patients (38.5%) who underwent completion axillary surgery has additional positive nodes. The two arms were well balanced according to the majority of main prognostic factors. Primary endpoint was axillary recurrence and secondary endpoints were overall survival (OS) and disease-free survival (DFS).

Results: Mean follow-up was 97 months (Q1-Q3 80-120). Axillary recurrence was 2.0% in cALND arm vs. 1.7% in RNI arm (P = 1.00). OS at 8 years was 77.9% vs. 84.8% (P = 0.060), and DFS was 72.1% in cALND arm and 77.4% after RNI (P = 0.51). The results show that RNI is statistically not inferior to cALND treatment.

Conclusions: The long term follow-up results of this prospective-randomized trial suggest that RNI without cALND does not increase the risk of axillary failure in selected patients with early-stage invasive breast cancer (cT $\leq$ 3 cm, cN0) and pN1(sn). Axillary radiotherapy should be an alternative treatment for selected patients with sentinel lymph node metastases.

Legal entity responsible for the study: The trial was approved by the National Institute of Oncology's Ethical Committee

Funding: None

Disclosure: All authors have declared no conflicts of interest.

167P Time to surgery in early breast cancer treated with neoadjuvant chemotherapy

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Background: A delay between surgery and adjuvant chemotherapy (CT) has been associated with worse outcome in early breast cancer (BC), but little is known about timing-related consequences in the neoadjuvant setting. Aim of this study is to investigate the impact of the interval between the end of neoadjuvant CT and surgery (CTTS).

Methods: This retrospective study analyzed a series of 469 consecutive BC patients (pts) receiving neoadjuvant CT at the Department of Oncology of Udine (n = 222) and of the Istituto Nazionale Tumori of Milan (n = 247), between 2004 and 2015. CTTS

was defined as the time between the last CT administration and surgery. Prognostic impact was investigated through Cox regression.

Results: Luminal-like subtype was the most frequent (53.69%) followed by HER2-positive (29.26%) and triple negative BC (17.05%). Median follow-up was 55.07 months (mo). Estimated overall survival (OS) at 24 and 60 mo was 96.4% and 88.2%, respectively. Estimated relapse free survival (RFS) at 24 and 60 mo was 83.6% and 65.8%. Median CTTS was 1.08 mo (25%-75% range: 0.89 - 1.2 mo). Among the total population no statistically significant differences were observed in terms of OS and RFS between CTTS $>$ 1 vs $<$ 1 mo (HR 1.18, 95%CI 0.72-1.98; HR 1.28, 95%CI 0.89-1.85, respectively). On multivariate analysis, grade 3 and Ki67 $>=$20% were associated with worse RFS (HR 2.09, 95%CI 1.31-3.33; HR 2.77, 95%CI 1.30-5.91, respectively); on the other hand, a pathological complete response was associated with better RFS (HR 0.23, 95%CI 0.09-0.56). In terms of OS, grading and Ki67 were marginally significant. Subgroup analysis for CTTS showed no statistically significant differences when stratification for the main clinico-pathological features was applied. Notably, a trend for interaction in the nodal status stratification was observed.

Conclusions: This study explored the impact on RFS and OS of the interval between the end of neaodjuvant CT and surgery. Notwithstanding the exploratory purpose, the results suggest that an interval superior to 1 month was not significantly detrimental in terms of both RFS and OS.

Legal entity responsible for the study: N/A

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Disclosure: All authors have declared no conflicts of interest.

168P Updated results of the Breast cancer task force phase II study of neoadjuvant weekly carboplatin (Cp) added to paclitaxel (P) followed by epirubicin (E) and cyclophosphamide (C) in triple negative breast cancer (TNBC) patients (pts)

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Background: Introduction: TNBC has the highest mortality of all BC subtypes. Neoadjuvant platinum added to the taxanes-antracycline chemotherapy has been reported to improve pathologic complete response (pCR) rate and survival in TNBC. Aim: To evaluate the efficacy and toxicity of the addition of weekly Cp to Pl and dose dense EC on the pCR rate in an open-label phase II study in stage II/III TNBC pts.

Methods: Patients and methods: Sixty three pts received dose dense P (80mg/m^2/wk) concurrent with Cp (AUC=2) for 12 wks, added to two-weekly E (90mg/m^2) and C (600mg/m^2) for 4 cycles, and followed by surgery and radiotherapy. The primary endpoint was pCR in the breast and axilla. Additionally adverse events are registered. A correlative assessment of germ line mutations in HRD genes is ongoing. Pts are monitored for clinical response by magnetic resonance and mammography and also for relapse free survival and time to treatment failure. The study sample size has been calculated according to the optimal Simon's two-stage design method. The target sample size was 63 patients with 80% power to detect a pCR rate of $>$ or $=$ 47% ($\alpha = 0.05$).

Results: Accrual to the study is completed and 63 eligible pts with operable, non-inflammatory stage II/III TNBC were included. Most pts were between 40 and 60 yr old and 49 out of 63 were stage T2. Forty percent were clinically node + and 68% were G3. Seventy three percent received breast conserving surgery. Thirty eight out of 63 pts (60%) achieved a pCR rate in the breast and axilla. In 52 evaluable pts for toxicity, the main toxicity for part 1 (Cp+P) of the combination was neutropenia G3/4 in 37 pts (71%) and for part 2 (EC) febrile neutropenia G3/4 in 18 pts (34%) despite primary prophylaxis, followed by thrombocytopenia G3/4 in 11 pts (21%). Only three pts had a neuropathy G3.

Conclusions: The addition of weekly carboplatinum to neoadjuvant dose dense paclitaxel and EC is feasible and a pCR rate in the breast and axilla as high as 60% in early TNBC pts is obtained. Correlation with genomic HRD deficiency is ongoing.

Clinical trial identification: 2014-003723-21; 28-02-2014

Legal entity responsible for the study: Breast Cancer Task force on behalf of the BSMO (Belgian Society of Medical Oncology)

Funding: Amgen and Teva

Disclosure: All authors have declared no conflicts of interest.

169P Neoadjuvant eribulin following anthracycline and taxane in triple negative breast cancer (HOPE): A multicenter, two stage, phase II trial

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Background: Neoadjuvant chemotherapy for triple negative breast cancer (TNBC) patients (pts) is mostly based on anthracycline and taxane (AT). The microtubule dynamics inhibitor eribulin mesylate (E) has been proved to increase survival in heavily pretreated metastatic breast cancer pts. We argue that sequential AT and E would benefit also non-metastatic TNBC pts.

Methods: Pts with primary TNBC$>$2 cm received doxorubicin 60 mg/m^2+paclitaxel 200 mg/m^2 day 1, q 21 for 4 cycles, followed by E 1.4 mg/m^2 days 1,8 q 21 for 4 cycles. The primary endpoint was the pathological complete response (pCR) rate; secondary endpoints included clinical response rate by RECIST 1.1, metabolic response by EORTC criteria, safety profile and biomarker analysis. Sample size was estimated to detect a 40% pCR, with 20% for a minimal hypothesis. With a type I error of 0.05 and a statistical power of 80%, 13 patients were to be initially enrolled. Observation of $\geq$ 4 pCR would justify continuation of accrual up to 43 pts.

Results: Thirteen pts were enrolled. The combination was safe with mostly G1/2 toxicities. The only G $\geq$ 3 event was neutropenia, which was related to AT in 4 pts and to E in 2 pts. An analysis of the degree of response by imaging was feasible in 11 pts. Overall 6/11 (54%) pts achieved a partial response after AT; of note 3/5 (27%) AT-unresponsive pts responded to E, 1 had stable disease and 1 pt definitely progressed. FDG PET/CT scans were available in 12 pts after AT and in 10 pts after 2 cycles of E. Median SUV_{max} values were 13, 3, and 2 at baseline, after AT and after E, respectively. Of the 4 pts with complete metabolic response (2 after AT and 2 after E), 2 achieved pCR at surgery. Immunostaining of paired pre- and post-treatment tumor bioptic specimens revealed reduction of beta-catenin, cyclin D and c-myc expression in the absence of n-cadherin modulation. The trial was halted because of the unmet primary endopoint (3 pCR).

Conclusions: Despite an unmet primary endpoint, E showed clinical and biological activity in TNBC pts. The observed modulation of beta-catenin pathway core proteins, purportedly outside the domain of epithelial mesenchymal transition, claims for further investigation and for the refinement in the definition of the clinical endpoints.

Clinical trial identification: EUDRACT: RELEASE: November 2012

Legal entity responsible for the study: Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

Funding: Eisai

Disclosure: All authors have declared no conflicts of interest.

170P Impact of neoadjuvant therapy (NT) and pathological complete response (pCR) on breast-conserving surgery (BCS) in patients (pts) with breast cancer (BC): A meta-analysis

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Background: We performed a meta-analysis of randomized trials that evaluated the pCR and surgical decisions after NT for BC.

Methods: Studies were retrieved by searching the PubMed database and the proceedings of major conferences. The primary outcome was BCS rate. Secondary outcomes were pCR rate and association to BCS. Meta-analyses were performed using random-effects (RE) models that use inverse-variance weighting for each treatment arm based on the number of evaluable pts. Point estimates are reported with 95% confidence intervals, and $p < 0.05$ was considered statistically significant.

Results: 36 studies were identified (N = 12,311 pts). 17/36 studies reported both pCR and BCT for at least 1 treatment arm, and comprise the studies in this analysis. The number of arms per study ranged from 1 to 6, such that 42 independent units were available to evaluate the association between pCR and BCT. The BCS rate ranged from

5% to 76% across arms with an average BCS of 57% (95% CI 52%-62%). Significant heterogeneity was observed among the trials (Cochrane Q = 787, p < 0.001, I^2 = 97%). In the meta-regression model, BCS rates were not significantly associated with year of first patient-in (p = 0.89), grade (p = 0.93), hormone-receptor status (p = 0.39). Clinical N-stage (p = 0.01) and HER2 status (p = 0.03) were significantly associated with BCS. pCR rate ranged from 3% to 60% across studies. The average pCR across all study arms was 24% (95% CI 19%-29%). No association was observed between pCR rate in a study arm and the resulting BCS rate in a univariate model (p = 0.34) nor after adjusting for HER2 and clinical nodal status (p = 0.82). Change in BCS with NT was further derived from the subset of 14 multi-arm trials, where 17 pairwise contrasts were made between randomized populations: 2 studies showed a significant difference in BCS. The difference in pCR rates between treatment arms ranged from -22% to 24%. However, no significant association is seen with the corresponding difference in BCS rates (p = 0.27).

Conclusions: This meta-analysis indicates that, despite increasing pCR, there is no concomitant increase in BCS. Future NT studies should reconsider using BCS as an endpoint.

Legal entity responsible for the study: Carmen Criscitiello

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Disclosure: All authors have declared no conflicts of interest.

171P Composite index of risk shows that benefit from adjuvant dose dense chemotherapy is not confined to triple negative breast cancer

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Background: Compared with the standard interval adjuvant chemotherapy, dose-dense schedule is proved to increase disease-free survival (DFS) in node-positive early breast cancer (EBC) patients (pts). To date, GIM2 is the only trial supporting the role of dose-dense chemotherapy in pts with hormone receptor-negative (HR-) or hormone receptor-positive tumours (HR+) (Del Mastro et al. Lancet 2015). To further refine the evidence of treatment effect in the HR+ subgroup, a composite index of risk was developed including clinico-pathological features.

Methods: The randomized phase III GIM2 trial enrolled 2091 pts with node-positive EBC (primary endpoint: DFS). A continuous, composite measure of treatment benefit was determined from a Cox model incorporating potential predictive factors (age: 25-40/41-55/56-71; histological grade: 1 + 2/3; HR status: positive/negative; ki-67 levels: ≤20%/>20%). Subpopulation treatment effect pattern plot methodology was used to reveal differential treatment effects on DFS according to composite index. The study analyzed the cohort of pts with HER2- (N = 1127) disease with a special focus on HR+ disease (N = 980).

Results: On average, the magnitude of benefit with dose dense chemotherapy versus standard chemotherapy widely varied according to composite measure of specific features. In the HER2- subgroup, the highest benefit was observed in pts with G3, HR-, >10 positive nodes, age <40 yrs, ki-67 > 20% (hazard ratio for DFS 0.57, 95% CI 0.35-0.94). Notably, among pts with HR+ disease, the following clinic-pathological characteristics conferred the highest benefit: G3, ≥4 positive nodes, age ≥56 yrs, ki-67 > 20% (hazard ratio for DFS 0.66, 95% CI 0.38-1.15).

Conclusions: Composite risk evaluation and corresponding subpopulation treatment effect pattern plot methodology suggest that benefit of dose dense adjuvant chemotherapy is not confined to triple negative EBC.

Legal entity responsible for the study: Gruppo Italiano Mammella

Funding: None

Disclosure: All authors have declared no conflicts of interest.

172P The prognostic impact of chemotherapy induced amenorrhea in women treated with early stage breast cancer

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Background: In this study; Amenorrhea caused by chemotherapy in early stage breast cancer patients and its effects on survival were investigated.

Methods: A total of 389 patients who received adjuvant chemotherapy from 600 premenopausal patients who were treated with early stage breast cancer during 2000-2013 and followed up were included in the study. Patients who did not undergo medical ovarian ablation (OA); Amenore as developing and non-developing, two groups were separated and compared with clinicopathologic features and survival. SPSS 17. version was used.

Results: Disease-free survival (DFS): median (m) 57 months (4-197 months), overall survival (OS): m 60 (10-168 months) and follow up time m 60 months (23-168 months). During follow-up, chemotherapy induced amenorrhea (CIA) was observed in 145 (57.5%) of 252 patients who did not have any ovarian ablation (OA. The 5-year OS rate of patients with CIA was significantly higher than the patients without CIA (p = 0.042, 95.9% vs 89.7 vs 158.88 vs 135.33 months, respectively). In the subgroup analysis, the OS in patients with CIA was significantly higher than in those without CIA in patients had HR (+) (p = 0.036, 97.5% vs 91.5 vs 162.13 vs. 136.20 months, respectively). There was no significant difference in the duration of OS between with CIA and without CIA of the patients who had not HR (+) (p = 0.736, 90.9% vs 86.8% and 126.16 and 133.76 months, respectively). The duration of OS was significantly longer in patients with CIA in the luminal A molecular subtype than in those luminal B molecular subtype, but the difference was not significant in patients without CIA (p = 0.027 vs p = 0.074 respectively).

Conclusions: The development of amenorrhea due to chemotherapy provides a significant survival advantage over those patients who do not develop amenorrhea due to chemotherapy. This advantage is more pronounced in hormone receptor positive, lymph node involvement and advanced disease. The development of amenorrhea due to chemotherapy in patients with HR negative does not affect survival. Amenorrhea development further prolongs survival compared to luminal B in the luminal A molecular subtype.

Legal entity responsible for the study: Istanbul Bilim University, Florence Nightingale Group of Hospitals

Funding: None

Disclosure: All authors have declared no conflicts of interest.

173P Determinants and outcomes associated with delays in adjuvant chemotherapy among breast cancer patients

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Background: Adverse outcomes have been associated with delays in the administration of adjuvant chemotherapy among breast cancer patients. We evaluate the determinants and outcomes associated with delays in time to chemotherapy (TTC) in a large cohort of older breast cancer patients.

Methods: We used the NCI-Surveillance Epidemiology and End Results (SEER) and Texas Cancer Registry (TCR)-Medicare linked data bases to identify patients ≥66 years old diagnosed with localized or regional breast cancer between 2001-2011. All patients received chemotherapy within 9 months of surgery. Delayed TTC was defined as > 90 days. Multivariable logistic regression was used to identify predictors of treatment delay. A Cox Proportional Hazards model was fit to determine the association between treatment delay, overall survival (OS) and breast cancer specific survival (BCSS).

Results: 25,096 patients were included, of them 2,676 (10.7%) had a TTC >90 days. In multivariable analysis factors associated with delays in TTC were: recent year of diagnosis (2011 vs 2001 OR = 1.31; 95%CI 1.03-1.67), older age (76-80 vs 66-70 OR = 1.51; 95%CI 1.33-1.72), black race (OR = 1.35; 95%CI 1.14-1.58), having state buy-in (as an indicator of poverty) (OR = 1.27; 95%CI 1.1-1.47), comorbidities (Charlson score 1 OR = 1.23;95%CI 1.09-1.37; score 2 OR = 1.57; 95%CI 1.37-1.81), mastectomy (OR = 1.49; 95%CI 1.33-1.67), mastectomy with immediate reconstruction (OR = 1.85; 95%CI 1.37-2.48), Oncotype DX testing (OR = 1.68; 95%CI 1.4-2.02), mastectomy >30 days after the initial surgery (OR = 16.91; 95%CI 12.07-23.68), brachytherapy (OR = 4.11; 95%CI 3.17-5.34) and whole breast radiation prior to

chemotherapy (OR = 31.9; 95%CI 28.05-36.49). After adjusting for potential confounders, patients with TTC >90 days had worse OS (HR = 1.37; 95%CI 1.27-1.48) and BCSS (HR = 1.34; 95%CI 1.19-1.51).

Conclusions: A delay in adjuvant chemotherapy administration >90 days is associated with adverse outcomes among older breast cancer patients. Determinants of delays were sociodemographic in nature, related to patient's characteristics and to treatment received. Every effort should be made to identify vulnerable patients and to administer chemotherapy in a timely manner.

Legal entity responsible for the study: The University of Texas MD Anderson Cancer Center

Funding: Susan G. Komen, CIPRIT

Disclosure: All authors have declared no conflicts of interest.

174P Adjuvant chemotherapy in pT1ab node-negative triple negative breast carcinomas: Results of a national multi-institutional retrospective study

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Background: Triple negative breast cancers (TNBC) are considered as associated with poor outcome, but prognosis of subcentimetric, node-negative disease remains controversial and evidence that adjuvant chemotherapy (CT) is effective in these small tumors remains limited.

Methods: Our objective was to investigate the impact of adjuvant CT on survival in pT1abN0M0 TNBC. Patients were retrospectively identified from a cohort of 22,475 patients who underwent primary surgery in 15 French centers between 1987 and 2013. Since rare pathological types may display very particular prognoses in these tumors, we retained only the invasive ductal carcinomas of no special type according to the last WHO classification witch is most common TNBC histologic type. End-points were disease-free survival (DFS) and metastasis-free survival (MFS). A propensity score for receiving CT was estimated using a logistic regression including age, tumor size, SBR grade, and lymphovascular invasion.

Results: Of a total of 284 patients with pT1abN0M0 ductal TNBC, 144 (51%) received post-operative CT and 140 (49%) did not. Patients receiving CT had more adverse prognostic features, such as tumor size, high grade, young age, and lympho-vascular invasion. Adjuvant CT was not associated with a significant benefit for DFS (Hazard ratio, HR = 0.77 [0.40-1.46]; $p = 0.419$, Log-rank test) or MFS (HR = 1.00 [0.46-2.19], $p = 0.997$), with 5-year DFS and MFS in the group with CT *vs.* without of 90% [81%-94%] vs. 84% [74%-90%], and 90% [81%-95%] vs. 90% [83%-95%], respectively. Results were consistent in all supportive analyses including multivariate Cox model and the use of the propensity score for adjustment and as a matching factor for case–control analyses.

Conclusions: This study did not identify a significant DFS or MFS advantage for adjuvant CT in subcentimetric, node-negative ductal TNBC. Although current consensus guidelines recommend consideration of adjuvant CT in all TNBC larger than 5 mm, clinicians should carefully discuss benefit/risk ratio with patients, given the yet unproven benefits.

Legal entity responsible for the study: SIRIC program (INCa-DGOS-Inserm 6038)

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Disclosure: All authors have declared no conflicts of interest.

175P OHERA: A real world study of cardiac events in > 3700 patients with her2-positive early breast cancer treated with trastuzumab: Final analysis

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Background: As of Sept 2016, > 2.2 million breast cancer (BC) patients (pts) have received trastuzumab (Herceptin®; H) in clinical trial or real world settings. Risk of cardiac failure in pts treated with H in real world practice may differ from that observed in a clinical trial setting.

Methods: OHERA (NCT01152606) is a non-interventional post-approval safety study that investigated incidence of symptomatic congestive heart failure (CHF) and cardiac death in pts with HER2-positive early BC (EBC) receiving adjuvant intravenous H (H IV) in routine clinical practice, per the EU Summary of Product Characteristics (SmPC). Pts with HER2-positive EBC (stage I–IIIb) considered for treatment with H IV per the EU SmPC were enrolled, treated and monitored per local practice. Primary endpoints were incidence of symptomatic CHF (New York Heart Association [NYHA] class II–IV) and incidence of cardiac death. Secondary endpoints included time to onset of CHF. The final analysis included pt data collected for up to 5 years or until death, loss to follow-up or consent withdrawal.

Results: Pts were enrolled Aug 2007–Nov 2010 at 199 sites across 9 countries. The safety population included 3733 pts with EBC treated with H IV. Median treatment duration was 11.8 months; median follow-up was 60.1 months. Incidence of symptomatic CHF was 2.8% (n = 106); including severe symptomatic CHF (NYHA class III–IV) in 1.0% (n = 38) pts. Median time to onset of symptomatic CHF was 5.7 months (95% CI 5.3–6.5) and 77 (72.6%) pts achieved CHF resolution. Incidence of cardiac death was 0.2% (n = 6). 251 pts had a left ventricular ejection fraction (LVEF) drop of ≥ 10% from baseline to < 50% and 169/251 (67.3%) achieved LVEF drop resolution. Incidence of CHF was higher in pts with baseline risk factors such as pre-existing cardiac conditions, age ≥65 years or baseline LVEF ≤55%. Pts who had left-side radiotherapy at baseline did not have higher CHF incidence.

Conclusions: OHERA is the largest study investigating the cardiac safety of adjuvant H IV in a real world setting to date. Final analysis results were consistent with cardiac safety results from previous adjuvant H IV clinical trials in EBC, and the baseline risk factors for CHF reported in the H IV EU SmPC.

Clinical trial identification: Protocol number: BO20652/RO 45-2317 ClinicalTrials.gov NCT01152606

Legal entity responsible for the study: F Hoffmann-La Roche Ltd

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176P Clinical outcomes of delayed start of trastuzumab treatment in patients with early breast cancer: ml25232 study

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Background: Breast cancer patients in low and middle income countries have limited access to targeted therapies such as trastuzumab. The discontinuous availability of trastuzumab created waiting lists and subsequent very delayed treatment. Since few studies have systematically analyzed possible deleterious effect of delayed trastuzumab treatment, we designed a study to investigate its consequences on overall survival and disease-free survival.

Methods: This was a multicenter cohort study of HER2-positive early breast cancer patients (n = 223) diagnosed between 01/05/2005 and 01/05/2010 in the Federation of Bosnia and Herzegovina. The study began in 01/01/2010, and enrollment was completed in 30/06/2012. Last follow up and cut off date for analysis was 31/03/2015.

Results: A total of 223 women (median 55 years; IQR: 49-61 years) were recruited. Since 131 (59%) patients waited for > 6 months after surgery to receive trastuzumab, we categorized our patient cohort into three groups: non-waiting group (n = 92; wait time < 6 months), and waiting group 1 (n = 85; wait time between 7 to 12 months) and waiting group 2 (n = 46; > 13 month wait). OS at 5 years in non-waiting group was 84%, compared to 72% in wait group 1 and 75% in wait group 2 ($p > 0.05$). DFS at 5 years in the non-wait group was 79%, compared to 65% in wait group 1, and 68% in wait group 2 ($p > 0.05$).

Conclusions: Unfortunate and unique circumstances in developing countries have created waiting lists for trastuzumab treatment—our systematic analysis of 223 women has shown that delayed start of trastuzumab treatment does not have a statistically significant effect on clinical outcomes, but shows a trend towards worse OS and DFS for women with delayed treatment. Thus, trastuzumab treatment has a persistent benefit even when administered with delayed start.

Clinical trial identification: ML25232

Legal entity responsible for the study: Roche

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177P Effects of neratinib (N) on health-related quality of life (HRQoL) in early-stage HER2+ breast cancer (BC): longitudinal analyses from the phase III ExteNET trial

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Background: The international, randomized, placebo (P)-controlled phase III ExteNET trial (NCT00878709) showed that N for 1 y after trastuzumab-based adjuvant therapy significantly improved 2-y invasive disease-free survival in early HER2+ BC patients (pts) (HR 0.67; 95% CI 0.50–0.91; p = 0.0091) [Chan et al. *Lancet Oncol* 2016]. Detailed longitudinal evaluation of HRQoL was an exploratory endpoint of ExteNET.

Methods: 2840 pts received N 240 mg/d or P for 1 yr. Pts completed FACT-B and EQ-5D questionnaires at baseline and months (M) 1, 3, 6, 9, and 12. Changes in scores from baseline were compared between groups using ANCOVA with no imputation for missing values. Sensitivity analyses using alternative methods were applied. Changes in HRQoL scores were considered to be clinically meaningful if greater than minimal clinically important differences (MCID) reported in the literature.

Results: 2407 pts were evaluable for FACT-B (N, n = 1171; P, n = 1236), and 2427 for EQ-5D (N, n = 1186; P, n = 1241). Compliance with questionnaires exceeded 85%. N was associated with decreased HRQoL scores at M1 *vs* P, after which between-group differences diminished (Table). They were consistently less than MCIDs, except for physical well-being (PWB) subscale at M1. BC subscale (BCS) showed small improvements with N at M3–M9, all less than MCIDs. Different sensitivity methods did not alter the results.

Table: 177P

Scale	MCID range	Adjusted† mean difference in change from baseline: N *vs* P				
		M1	M3	M6	M9	M12
FACT-B total	7–8	−2.9*	0.1	−0.6	−0.5	−0.8
TOI-PFB	5–6	−2.6*	−0.3	−0.7	−0.4	−1.0*
TOI-ESB	5–6	0	1.2*	0.6	0.5	0.4
PWB	2–3	**−2.4***	−1.1*	−1.0*	−0.9*	−1.1*
BCS	2–3	0.3	0.7*	0.4*	0.6*	0.2
EQ-5D index	0.09–0.10	−0.02*	−0	−0	0	0
EQ health state	7–10	−2.7*	0.1	−1.3*	−0.7	−0.4

†For baseline score;

*Statistically significant at $p < 0.05$ without adjustment for multiple testing
TOI = trial outcome index; PFB = PWB + functional WB + BCS; ESB = emotional WB + social WB + BCS.

Conclusions: N was associated with decreased HRQoL, in particular in PWB, at M1, possibly due to N-related diarrhea. Based on their small magnitude, differences observed after M1 in PWB favoring P and in BCS favoring N, may not be clinically important.

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Legal entity responsible for the study: Wyeth, Pfizer and Puma Biotechnology

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178P Second interim analysis of HerSCin, a German non-interventional study of subcutaneous trastuzumab for HER2-positive early breast cancer in routine clinical practice

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Background: Compared with IV trastuzumab, subcutaneous trastuzumab (H_{SC}) showed non-inferior outcomes in the HannaH trial and was preferred by patients (pts) and healthcare professionals in the PrefHer study. The ongoing HerSCin study (NCT01959386) is evaluating H_{SC} in routine clinical practice in Germany.

Methods: Pts with HER2-positive early breast cancer treated with (neo)adjuvant H_{SC} (investigator's chosen regimen) in routine oncology practice between Nov 2013 and Nov 2016 were eligible. Pts could be enrolled retrospectively up to 9 wks after starting H_{SC}. Baseline characteristics, treatment, adverse events (AEs), clinical outcomes and quality of life (EORTC QLQ-C30/QLQ-BR23) data are collected prospectively. Primary efficacy endpoints are pCR rate (neoadjuvant setting) and 2-year disease-free survival (adjuvant setting).

Results: At the data cut-off for the second planned interim analysis (Nov 2016), 420 of 1003 pts enrolled to date from 103 German centres had completed therapy and were eligible for analysis. The median duration of follow-up was 12.2 (range 3.3–25.8) mo. Baseline characteristics are below. The mean duration of H_{SC} was 8.8 mo (neoadjuvant: 9.2; adjuvant: 8.7). All-grade and grade ≥3 AEs were reported in 63% and 15% of pts, respectively. The most common all-grade AEs were fatigue (10%), diarrhoea (9%) and arthralgia (7%). AEs led to treatment interruption/withdrawal in 48 pts (11%). Only 1 of the 4 fatal AEs was considered treatment related (cardiac/respiratory failure). The pCR rate (including carcinoma in situ) in the neoadjuvant subgroup was 60.3% (95% CI 48.5–71.2). Efficacy results in the adjuvant subgroup are not mature.

Conclusions: The 60.3% pCR rate is consistent with prospective trials of IV trastuzumab and H_{SC}. Tolerability is as expected based on results from randomised trials. H_{SC} is an active, feasible and tolerable treatment for use in routine oncology practice as well as the clinical trial setting.

Clinical trial identification: NCT01959386

Legal entity responsible for the study: Roche Pharma AG

Funding: Roche Pharma AG

Disclosure: S. Kümmel: Membership on advisory board or board of directors: Roche Pharma AG.

S. Busch-Liles: Employment: Roche Pharma AG.

M. Schmidt: Membership on advisory board or board of directors: Novartis, Pfizer, Pierre-Fabre, Roche. Corporate-sponsored research: Pierre-Fabre.

All other authors have declared no conflicts of interest.

Table: 178P

Parameter, No. of pts (%)		All pts (n = 420)	Neoadjuvant subgroup (n = 78)	Adjuvant subgroup (n = 342)
Median age, years (range)		56 (20–90)	52 (20–77)	57 (27–90)
ECOG performance status	0	258 (61)	44 (56)	214 (63)
	1	116 (28)	26 (33)	90 (26)
	2	10 (2)	1 (1)	9 (3)
	Missing	36 (9)	7 (9)	29 (8)
Cardiac conditions at baseline	Arterial hypertension	134 (32)	24 (31)	110 (32)
	Coronary heart disease	14 (3)	3 (4)	11 (3)
HER2 status by IHC	0/1+	3 (1)	0	3 (1)
	2+	104 (25)	13 (17)	91 (27)
	3+	310 (74)	65 (83)	245 (72)
	Missing	3 (1)	0	3 (1)
Histological grade	1	7 (2)	0	7 (2)
	2	184 (44)	30 (38)	154 (45)
	3	222 (53)	46 (59)	176 (51)
	Missing/unknown	7 (2)	2 (3)	5 (1)
Subtype[a]	Ductal	343 (82)	65 (83)	278 (81)
	Lobular	24 (6)	3 (4)	21 (6)
	Other	54 (13)	10 (13)	44 (13)
Positive nodal status		161 (38)	25 (32)	136 (40)
Hormone receptor status	ER positive	280 (67)	42 (54)	238 (70)
	PgR positive	234 (56)	39 (50)	195 (57)
	ER and PgR negative	127 (30)	31 (40)	96 (28)

[a]One patient (adjuvant setting) recorded as both ductal and lobular. ER=oestrogen receptor; IHC=immunohistochemistry; PgR=progesterone receptor.

179P Timing of initiation of trastuzumab (T) and long-term outcome of patients (pts) with early-stage (ES) HER2-positive (HER2+) breast cancer (BrCa): Impact of neo-adjuvant (NAdj) versus adjuvant (Adj) strategy

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Background: The optimal schedule of anti-HER2 Tx for HER2+ ESBrCa with respect to chemotherapy and surgery remains undefined. We performed a retrospective analysis of a large, prospectively maintained single institution data base to study the impact of treatment schedule on clinical outcome.

Methods: Our database included all pts treated with T for Stage I to III HER2+BrCa who had a minimum follow up (FU) of 3 years. Time-to-first-T (TFT) was calculated from the date of the first diagnostic breast biopsy to the date of the first T. Pts with stage N3b and N3c or inoperable disease were excluded from the study.

Results: A total of 506 pts treated between October 2001 and March 2014 were included in the study. T was administered as part of AdjTx in 386 (76%) pts, and of NAdjTx in 120 (24%), 338 (67%) pts had TCH [docetaxel/CBDCA/T] or "TCH-like", 119 (24%) pts had delayed concomitant (i.e. AC-TH)/sequential T. Median FU is 73.3 months (range 1.4-176.3). Median TFT for the overall cohort was 12 weeks (range 1.9-122.3). Median TFT was significantly shorter in the NAdj than in the Adj cohort: 4.4 vs 14 weeks [$p<0.00001$]. In the entire cohort, DFS and OS rates were 83% and 91%, respectively. DFS and OS rates were 90% and 96% vs 75% and 85% for pts with TFT $\leq$12 weeks vs TFT >12 weeks, respectively [$p < 0.0001$]. Pts with TFT >12 weeks had a significantly higher risk of recurrence [HR 1.96; $p = 0.008$] and death [HR 2.84; $p = 0.006$] than pts with TFT $\leq$12 weeks. Pts with positive lymph nodes (LN+) and TFT >12 weeks had significantly higher risk of relapse [HR 2.40, $p = 0.001$] and death [HR 2.10, $p = 0.024$] than pts with TFT $\leq$12 weeks. However, despite NAdj pts having significantly higher rate of LN + (75% vs 53%, $p < 0.0001$), DFS and OS were superimposable in the two cohorts. Pts with LN+ had superior DFS when treated with NAdjTx compared with AdjTx [$p = 0.006$].

Conclusions: Our mature data indicate that timing of anti-HER2 Tx significantly affects long-term outcome and T should be initiated $\leq$12 weeks from first diagnosis of ES HER2+BrCa. The early institution of T in the NAdj cohort abolished the negative impact of LN+, thus suggesting that this should be considered the optimal Tx strategy for ES HER2+BrCa.

Legal entity responsible for the study: Giuseppe Gullo

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Disclosure: All authors have declared no conflicts of interest.

180P Adjuvant endocrine treatment: Stop or continue?

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Background: There is currently a trend towards extending adjuvant endocrine treatment in higher risk breast cancer patients up 10 years. However, a trade off has to be made between persisting side effects of endocrine treatment vs a small advantage in recurrence risk. It is not well known if patients still suffer side effects after 5 years of endocrine treatment, and if these may be reversible. Therefore, we studied the change in side effects of endocrine treatment and overall quality of life during and 3 months after cessation, in patients who completed at least 5 years of treatment.

Methods: We included 101 patients from 2 oncological practices who underwent curative treatment for breast cancer and whose adjuvant endocrine therapy ended between 2013 and 2016. Patients willing to cooperate filled out a questionnaire before and 3 months after stopping their endocrine therapy. Hot flashes, joint pain, muscle pain and fatigue were scored as absent, a little, severe or very severe. Overall quality of life was scored on a scale from 0 to 10.

Results: 101 patients were included. Average was 61 years. Tumors were T1-T4, N0-N3, M0. Most patients received tamoxifen for 2-3 years, followed by an aromatase-inhibitor for 3-6 years. The main finding of this survey is that overall quality of life improved significantly after stopping endocrine therapy from 6.9 (range 4-10) to 7.7 (5-10) ($p < 0.01$ Wilcoxon paired rank test). 22 women improved $\geq$2 points. Patients who scored high on muscle aches and joint complaints improved the most.

Conclusions: Even patients who completed at least five years of endocrine treatment suffer side effects up to the end of treatment. After cessation these ameliorate in many, and this improves quality of life significantly. These findings are relevant when deciding

on extended adjuvant endocrine treatment in individual patients. Detailed analysis will be presented.

Clinical trial identification: Under Dutch law no obligations for protocol submission for this type of survey, only institutional approval.

Legal entity responsible for the study: E.W. Muller

Funding: None

Disclosure: All authors have declared no conflicts of interest.

181P Use and effectiveness of adjuvant ovarian function suppression (OFS) in premenopausal women with early breast cancer

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Background: OFS either in association with tamoxifen (TAM) or an aromatase inhibitor (AI) improved disease-free survival in young women ($\leq$35) and in those premenopausal women at higher risk of recurrence. However, its survival benefit remains largely unknown. In this study we characterize real-world use of adjuvant OFS from 2006 to 2015 and analyze its overall survival (OS) impact.

Methods: Retrospective observational cohort study of premenopausal women with Stage I-III hormone receptor-positive (HR+) breast cancer treated at one of 5 large centers in Portugal and diagnosed from 2006-2015. Study outcomes were use of OFS and OS. Pearson's Chi^2 test, logistic regression and Cox proportional hazards models were used.

Results: Of 1717 eligible patients, 304 (17.3%) were treated with adjuvant OFS, of which 271 (15.4%) in combination with TAM and 33 (1.9%) with AI. Baseline characteristics differed by subgroups: patients treated with OFS were younger, had larger, less differentiated (grade III 16% vs 24% for OFS), more frequently HER2 positive (14% vs. 19% for OFS) tumors, and underwent more frequently mastectomy (48% vs 57% for OFS), radiotherapy (25% vs 31% for OFS) and (neo)adjuvant chemotherapy (73% vs 79% for OFS). Adjuvant OFS was used at least since 2006 with an increase in its use from 2014 onward (16% vs 25% since 2014), particularly for the combination with AI (0.4% vs 8% since 2014). In a multivariate model, characteristics associated with use of OFS included younger age and year of diagnosis $\geq$2014 (both $p < 0.001$). Median time on OFS was 25 mo. (interquartile range 21-27). With a median follow-up of 38 mo. (IQR 20-66) and after controlling for age at diagnosis, staging, histologic grade, HER2 status, use of (neo)adjuvant CT, type of surgery and year of diagnosis, patients treated with OFS had a better OS when compared to those not treated with OFS (adjusted-HR 0.44, 95% CI 0.19-0.96; $p = 0.040$). Absolute benefit at year 5 was 2.1% (93.2 [95% CI 90.8 – 94.9) vs 95.3 [95% CI 89.7 – 97.9]).

Conclusions: In the real-world setting, a quarter of premenopausal women with early breast cancer were already treated with adjuvant OFS in 2014. After a median follow-up of 3 years, adjuvant OFS showed an OS benefit.

Legal entity responsible for the study: Hospital de Santa Maria, Centro Hospitalar de Lisboa Norte

Funding: None

Disclosure: All authors have declared no conflicts of interest.

182P A phase II randomised study of Adjuvant hypo-fractionated radiotherapy with concurrent vs sequential letrozole in post-menopausal women with hormone receptor positive breast cancer: Report of pulmonary toxicity and cosmetic outcome

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Background: The sequence of hormonal therapy with adjuvant radiation(RT) is debated because of anticipated morbidity. We conducted a phase II study to evaluate feasibility and efficacy of concurrent and sequential letrozole along-with hypo-fractionated RT(HFRT).

Methods: A total of 50 Post-menopausal women with hormone-receptor positive, Stage I-III Breast cancer received adjuvant HFRT 42.5Gy/16fr/3weeks and were randomly assigned to either concurrent (arm A) or sequential letrozole (arm B). Letrozole was started 3 weeks before RT in the concurrent, and 3 weeks after RT in sequential group. Pulmonary toxicity was assessed by clinical examination, chest x-ray, pulmonary function tests and HRCT chest (if indicated) at baseline, at one and six months(m) post RT. Cosmetic outcome was reported in both arms with six parameters (Table) at 6 m post RT.

Results: A total of 48 patients(pts) were followed up for 6 m (25 in Arm A and 23 in Arm B). None of the pts developed acute pulmonary toxicities. Mean (R) FeV1 and FVC values at baseline, 1 and 6 m post RT were 1.8 l (1.6-1.9) and 2.2 l(2.1-2.4), 1.79 l(1.5-1.9) and 2.1 l(1.9-2.4) and 1.85 l(1.6-2) and 2.2 l(2-2.4) respectively, and were comparable. FeV1 and FVC remained within 80 to 120% of the baseline values in 37 pts (20 Arm A vs 17 Arm B, $p = 0.5$). FeV1 and FVC were reduced by more than 80% at 6 m in 3 pts of Arm A and 5 pts in Arm B, ($p = 0.7$), while this was improved by over 120% in 5 pts (2 vs 3, $p = 1$). RTOG grade 2-3 radiation dermatitis was seen in 33 pts (15 vs 18, $p = 0.55$) while 5 pts had grade 4 toxicity (2 vs 3, $p = 1$). There was no treatment interruption because of toxicity.

Table: 182P

Cosmetic Outcome

	Mild change		Marked change	
	ARM A	ARM B	ARM A	ARM B
Breast Shrinkage	6	5	2	3
Breast Hardness	2	2	1	0
Breast Swelling	1	0	0	0
Change in Skin appearance	9	8	3	3
Self-breast assessment	14	13	5	5
Photographic breast assessment	15	15	3	2

Overall, 18 pts had excellent cosmesis (7 vs 11, $p = 0.4$) while 32 had good cosmesis. (18 vs 14, $p = 0.4$).

Conclusions: HFRT along-with concurrent Letrozole is well tolerated. However, patients are being followed to assess loco-regional disease control and late toxicities.

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Disclosure: All authors have declared no conflicts of interest.

183P Intrinsic tumor features underlying clinical subtype discordance in early breast cancer

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Background: Despite efforts for laboratory and method harmonization, discordant clinical subtypes for ER/PgR/HER2 that determine treatment selection for breast cancer patients in clinical practice, still pose a challenge.

Methods: We investigated the clinical relevance of discordant clinical subtypes and their clinicopathological and genotype characteristics (60-gene panel) in a series of 1427 breast cancer patients treated within 4 adjuvant trials (2 in the pre- and 2 in the post-trastuzumab era; recruitment period 1997 – 2012). Treatment decisions were based on local laboratory typing; all tumors were re-typed centrally. Disease-free survival was assessed.

Results: We observed 340 (23.8%) discordant tumors for ER/PgR and/or HER2, ranging from 30% in the oldest to 19% in the most recent trial ($p = 0.004$); Cohen's K was 0.512 for all subtypes, 0.583 for ER/PgR and 0.687 for HER2. ER/PgR discordance was associated with ER ($p < 0.001$) and PgR ($p = 0.017$) heterogeneity, basal phenotype, as well as higher grade, TILs and Ki67 labeling (all $p < 0.001$). HER2 discordant tumors had lower HER2 gene and CEN17 copies, and lower HER2/CEN17 ratios (all $p < 0.001$). Triple-positive tumors were rarely (0.5%) retyped as triple-negative (TN). ER/PgR discordant tumors had mutation patterns resembling HER2+ and TN, e.g., inversed TP53 and PIK3CA mutation prevalence ($p < 0.001$). Mutation clustering and phylogenetic analysis distinguished between concordant ER+/PgR+/HER2- tumors (73% of all tumors) and all other subtypes, with strong associations between ER±/PgR±/HER2- and ER+/PgR+/HER2 ± ($p < 0.001$). More relapses were noticed in patients with ER/PgR and HER2 negative-to-positive cases who did not receive hormonotherapy and trastuzumab (multivariate $p = 0.048$ and $p = 0.016$, respectively), but not in positive-to-negative cases.

Conclusions: Apart from technical considerations, clinical subtype discordance may reflect the genetic background of breast cancers, which appear to evolve by deviating from the ER+/PgR+ status. Development and reporting of phenotypic surrogates

predictive of discordance is needed for increasing diagnostic accuracy and appropriate treatment selection.

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184P Distribution of genomically defined recurrence risk in luminal A and B breast tumors defined by inmunohistochemistry: A retrospective study in Spanish population

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Background: Semiquantitative inmunohistochemical (IHC) expression of progesterone receptor (PR) adds prognostic value to the current IHC-based luminal A (LA) definition, such that patients (pts) with LA (Ki67 <14% and PR > 20%) tumors can be spared from adjuvant chemotherapy (CT). Oncotype Dx® (ODX) and MammaPrint® (MP) assays have been validated as predictors of CT benefit. This study assessed the distribution of recurrence risk in LA and LB breast tumors as defined by Ki67 and PR.

Methods: A retrospective analysis was performed in 889 T1-2, N0-Nmic, M0 tumors for which ODX or MP results and local pathology data were available. Ki67 was assessed by IHC (high ≥14% and low <14%). PR was assessed by semiquantitative IHC (PR low < or = 20%, high >20%). Histological grade was defined using the Nottingham grading system.

Results: Median age 54 years (18-77). All pts had HER2 negative tumors. Median tumor size 15 mm (2-88). Three hundred (33.7%) tumors were classified as LA and 589 (66.3%) as LB. Grade 1 tumors were higher in LA (27%) than in LB (19%) pts (p < 0,001). CT was first recommended in 137 pts (45.7%) with LA vs. 361 pts (61.3%) with LB tumors. ODX was performed in 432 (48.6%) pts and MP in 457 (51.4%). Recurrence risk distribution varied significantly between groups (p < 0.001). ODX: among LA pts, 71.4%, 25.7% and 2.9% had low, intermediate and high recurrence risk respectively; among LB pts respective values were 46.2%, 44.2% and 9.6%. MP: among LA pts, 81.2% and 18.8% had low and high recurrence risk, respectively; among LB pts respective values were 54.2% and 45.8% (Table). After test results CT was recommended to 61 pts (20.3%) with LA vs. 268 pts (45.5%) with LB tumors.

Table: 184P

Recurrence Risk (%) ODX (n = 432)	LA (n = 300)	LB (n = 589)
Low	71.4	46.2
Intermediate	25.7	44.2
High	2.9	9.6
MP (n = 457)		
Low	81.2	54.2
High	18.8	45.8

Conclusions: There is a wide distribution of recurrence risk results between LA and LB tumors defined by Ki67 and PR which confirms the important role of gene-expression assays in adjuvant decision making. Of note about half of pts with LB tumors had low recurrence risk indicating minimal benefit from adjuvant CT.

Legal entity responsible for the study: Ministry of Health of the Community of Madrid (Spain)

Funding: Ministry of Health of the Community of Madrid (Spain)

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185P The first report of multicenter validation study of 95-gene classifier, a multi-gene prognostic assay of estrogen receptor positive and node negative breast cancer patients

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Background: 95-Gene Classifier (95GC; Curebest™ 95GC Breast) is one of the multi-gene prognostic assays of estrogen receptor (ER) positive and node negative breast cancer patients, developed 95 gene-set without overlap with that used in another RT-PCR based product (Oncotype DX®). According to the original paper, the prognostic capability of 95GC has been shown even in the "intermediate" patients by microarray-based simulation model, "Recurrence Online", of above RT-PCR product. But still 95GC has been validated only using the data from single institute and public database. Here we report the result of the first multi-center validation study for this multi-gene assay.

Methods: ER-positive and T1-2/N0/M0 breast cancer patients who received only hormonal therapy, without chemotherapy, in adjuvant were enrolled retrospectively. For each patient, fresh frozen tissue was applied to the assay and the classification result of 95GC, "L" or "H", was used for the validation on 5 year recurrence free survival (5Y-RFS).

Results: We analyzed 75 eligible cases out of 150 enrolled, and found 47 patients classified as "L" showed 96.5% of 5Y-RFS (95%CI:89.5-98.9) while 28 patients of "H" showed 79.1% of 5Y-RFS (95%CI:63.8-88.5). There was a statistically significant difference between RFS of "L" and "H" groups by Log-Rank test (p = 0.0017). Other factors having significant association with 95GC were histological grade (p = 0.0012), "Recurrence Online" (p < 0.001) and "PAM50" (p < 0.001). And the patients of histological grade 2, of intermediate group by "Recurrence Online" and of Luminal B by "PAM50" could be classified into "L" and "H" by 95GC with different trends of RFS.

Conclusions: 95GC was well validated by this first multi-centered retrospective study on 5Y-RFS of ER-positive, node-negative patients who received only hormonal therapy in adjuvant. The result indicates the usefulness of this novel multi-gene assay, as it can classify target patients into 2 groups, "L" and "H", according to the prognosis of 5Y-RFS.

Legal entity responsible for the study: Takayuki Kinoshita

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Disclosure: All authors have declared no conflicts of interest.

186P Breast cancer PAM50 subtypes: Correlation between RNA-Seq and multiplexed gene expression platforms

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Background: Gene expression signatures are a key tool for decision-making in breast cancer. In 2000 Perou *et al.* identified 4 intrinsic subtypes of breast cancer from gene expression data: LumA, LumB, HER2-enriched and Basal-like. These breast cancer subtypes yielded a superior prognostic impact than classical immunohistochemistry factors. From the initial intrinsic subtype, a 50-gene signature was developed for subtype assignment. PAM50 is being successfully used in multiplexed gene expression platforms such as NanoString nCounter®, which is the basis for the Prosigna® test. The

latter was approved for the risk of distant relapse estimation in postmenopausal women with hormone receptor+, node+/- early stage breast cancer patients; and is a daily-used tool assessing the need of adjuvant chemotherapy.

Methods: The analyses were performed in paraffin embedded tissues (FFPE) from 96 patients recruited in a multicenter, prospective, non-randomized triple negative breast cancer trial (NCT01560663). Pre-treatment core biopsies were performed following clinical practice guidelines and conserved as FFPE for further RNA extraction. PAM50 was performed on both NanoString nCounter® and RNA-Seq technologies. Subtype assignment was based on the nearest centroid classification following this procedure for both platforms.

Results: Subtype calling agreed on 96% of the cases (NanoString nCounter®/RNA-Seq discordances: 3 Basal-like/HER2-enriched and 1 HER2-enriched/LumA). Both the Spearman correlation to each of the centroids and the risk of recurrence (ROR) were above 0.89 in both platforms. Furthermore, the agreement on proliferation score reached up to 0.97. In addition, 82% of the individual PAM50 genes showed a correlation coefficient >0.80.

Conclusions: The RNA-Seq is a fundamental research tool for whole transcriptome analysis. However, it cannot be massively used in the daily clinical practice, due to its processing time requirements and economic costs. We demonstrated that the RNA-Seq technology provides similar results to the NanoString nCounter®, with the latter providing lower cost and more simplicity in its use.

Clinical trial identification: NCT01560663

Legal entity responsible for the study: Instituto de Investigación Sanitaria Gregorio Marañón (IiSGM)

Funding: None

Disclosure: All authors have declared no conflicts of interest.

187P Summary of head-to-head comparisons of patient (pt) risk classifications by the 21-gene recurrence score (RS) assay and other genomic assays for early breast cancer (EBC)

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Background: Many genomic assays that assess recurrence risk in EBC are prognostic, but they differ in risk group stratification, which can affect clinical utility. Prospective outcomes of > 50K pts treated based on 21-gene RS results have shown that pts with low RS EBC can safely forgo chemotherapy. Because of its extensive validation and wide clinical use, the RS assay is a common comparator in head-to-head studies with other assays.

Methods: Published/presented studies of the RS assay performed on same tumor samples with Breast Cancer Index (BCI), EndoPredict (EP) or EP+clinical features (EPclin), MammaPrint (MMP), and/or Prosigna (ROR) assays were reviewed. Study findings were summarized descriptively.

Results: 14 studies were found that compared the RS assay with BCI (1), BCI, EPclin, and ROR (1), EP/EPclin (2), MMP (6), and ROR (4). Overall discordance in risk stratification ranged from 43% to 66% between assays (Table). The RS assay classifies 12% of pts as high risk, compared with EP (63%), EPclin (48%), and MMP (46%), assays with low/high risk groups, and compared with BCI (16%) and ROR (33%), assays that, like the RS assay, use three risk groups.

Conclusions: The five most common genomic assays in clinical use for EBC risk-stratify pts differently and thus are not interchangeable. Of these, the RS assay classifies the smallest proportion of pts as high risk.

Legal entity responsible for the study: Zsuzsanna Varga

Funding: Genomic Health

Disclosure: Z. Varga: Consultant/advisor: Genomic Health, Roche. P. Sinn: Advisor: Genomic Health. D. McCullough, A. Lau, M.C. Stöppler, F.L. Baehner, C. Chao: Employment and stock ownership: Genomic Health. A. Seidman: Consultant/speaker: Genomic Health.

188P The impact of Oncotype DX breast cancer assay results on clinical practice: A UK experience

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Background: Gene expression profiling is increasingly being used by clinicians to help determine whether or not to offer adjuvant chemotherapy. Oncotype DX is a 21 gene panel developed to predict the risk of tumour recurrence in patients with oestrogen receptor (ER) positive, HER2 negative breast cancer. NICE has recommended its use for patients at intermediate risk of recurrence, where this information would help clinicians to assess the potential benefit of chemotherapy versus endocrine therapy alone. Our aim was to see how oncologists are interpreting Oncotype DX tests in their clinical practice.

Methods: Data on patient and tumour characteristics (size, grade, ER/PR/HER2/nodal status), Oncotype DX recurrence score, treatment options offered and treatment outcomes were collected from 14 cancer centres across the UK.

Results: Of the 628 patients tested, 317 (50%) were in the low risk category (recurrence score <18), 224 (36%) were intermediate risk (score 18-30) and 81 (13%) were high risk (≥31). Chemotherapy was recommended for 52 patients in the low risk group, and was discussed/offered to a further 21. Chemotherapy was recommended for 91.8% of high risk patients. For patients with intermediate Oncotype scores, chemotherapy was

Table: 187P

Discordance[a] Between the RS Assay and Other Assays

	BCI			ROR			EP/EPclin			MMP		
Study[b]	1-level	2-level	Overall	1-level	2-level	Overall	1-level	2-level	Overall	1-level	2-level	Overall
Sestak 2016	37%	5%	42%									
Bartlett 2016[c]				40%	10%	50%						
Alvarado 2015				37%	10%	46%						
Dowsett 2013				41%	3%	43%						
Sinn 2017				45%	20%	66%						
Varga 2013							29%/29%	18%/21%	47%/50%			
Clough 2013										38%	19%	57%
Denduluri 2011										34%	25%	58%
Maroun 2015										31%	22%	53%
Shivers 2013										26%	19%	44%

a. Overall=any discordance in risk classification between the RS assay and other; 1-level=discordance of one risk category (low ↔ intermediate or intermediate ↔ high); 2-level=discordance of two risk categories (low ↔ high). b. Four studies lacked risk classification information appropriate for inclusion in this table. c. Study used nonstandard RS cutoffs for the RS vs. MMP comparison.

recommended for 101 patients (45.9%), the option of chemotherapy was discussed/offered to 31 (14.1%) and 88 (40.0%) were not offered chemotherapy. Overall, 160 patients (25.9%) received chemotherapy. Where oncologists recommended chemotherapy to patients (n = 231), 59.7% of patients went on to receive chemotherapy. Where oncologists had offered or discussed chemotherapy as an option (n = 58), 27.6% of patients went on to receive it. The most common regimes were FEC75x6 (23.9%), ECx6 (13.8%) and ECx4 (9.4%), with 13.2% of patients receiving 3rd generation chemotherapy (FEC/T, TC or EC/taxane); other regimes included ACx4, TCx4 and weekly paclitaxel.

Conclusions: Throughout the UK, about half of patients tested had low risk Oncotype scores and the majority (74.1%) of patients tested did not receive chemotherapy. The widest variation in clinical practice was observed in interpreting intermediate risk Oncotype results, and in the chemotherapy regimens offered.

Legal entity responsible for the study: Judy King

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Disclosure: All authors have declared no conflicts of interest.

189P Enhancing decision-making about adjuvant chemotherapy in ER+, HER2- early breast cancer (EBC) following EndoPredict testing

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Background: Chemotherapy side-effects can be substantial. There is increasing recognition that with surgery, radiotherapy and hormone treatment (tmt), many patients (pts) derive no benefit from chemotherapy and experience only iatrogenic harm. Gene expression profiling tests can help refine recurrence risk and likely chemotherapy benefit. EndoPredict is a multigene test which includes clinico-pathologic parameters to produce an EPclin score classifying risks of distant recurrence as low or high for ER+ve HER_2–ve pts treated with adjuvant endocrine tmt alone. We compared tmt decisions pre and post EndoPredict test results, pts' anxiety, decisional conflict and oncologists' confidence about decisions made.

Methods: 14 oncologists in 7 UK hospitals saw 149 pts judged to have equivocal indications for chemotherapy. Pts and oncologists discussed provisional tmt decisions based on usual prognostic factors. These decisions were reconsidered when EPclin results were available. Pre and post-test pts completed Spielberger's State/Trait Anxiety inventory (STAI) and a decision conflict scale (DCS). Oncologists additionally recorded:- basic clinical details, their agreement with, and confidence about tmt decisions (endocrine (E) therapy +/- chemotherapy(C)).

Results: 66.7% pts with an initial E alone decision and a high risk result upgraded to E+C. 9.4% pts with initial E+C decisions and high risk results down-graded to E alone. None of 46 pts initially favouring E alone who were low risk changed decisions. 82.8% who initially wanted E+C and had low risk scores downgraded to E alone. Endopredict results increased oncologists' confidence (8% 'strongly agreed' pre-test, 50% post-test). Oncologists neither agreeing nor disagreeing with decisions fell (24% to 5%). Anxiety was stable in pts with unchanged decisions. Pts whose tmt was downgraded had significantly lower anxiety scores ($p < 0.01$); those whose tmt was upgraded had increased scores ($p < 0.001$). Likewise overall uncertainty on DCS fell post-test ($p < 0.023$).

Conclusions: EndoPredict scores increased oncologists' and pts' decision-making confidence, generally improved the matching of risk with therapy decisions.

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Legal entity responsible for the study: David Bloomfield

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190P Circulating ESR1 mutations at the end of aromatase inhibitor adjuvant treatment and after relapse in breast cancer patients

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Background: Detection of *ESR1* circulating mutations is associated with acquired resistance to aromatase inhibitor (AI) in metastatic breast cancer. Until now, the presence of *ESR1* circulating mutations at the end of the adjuvant treatment by AI in early breast cancer had never been clearly established. In this context, the aim of the present study was to evaluate the *ESR1* circulating mutation frequency at the end of adjuvant treatment in patients with a subsequent local or metastatic relapse.

Methods: This monocentric retrospective study was based on available stored plasmas and included all early breast cancer patients who completed at least 2 years of AI adjuvant treatment and experienced a documented relapse at least 6 months after the end of their treatment. *ESR1* circulating mutations (D538G, Y537S/N/C) were detected by droplet digital PCR in plasma samples taken both at the end of adjuvant treatment and on AI progression in patients re-exposed to AI during the metastatic phase.

Results: A total of 39 patients were included, with a median adjuvant AI exposure of 60 months (range 41-85). One patient (2.6%) had a local relapse only, while all the others (97.4%) had a metastatic relapse during follow-up. Median delay between the end of adjuvant treatment and relapse was 25 months (range 6-71). No ESR1 circulating mutation was detectable at the end of AI adjuvant therapy. In contrast, among the 25 patients (64%) who progressed on AI during the metastatic setting, 17 plasma samples were available and 7 patients (41,2%) had a detectable mutation.

Conclusions: Our results highlighted that there is no emergence of circulating *ESR1* mutation at the end of an AI-based adjuvant treatment in hormone receptor positive breast cancer patients. In contrast, and as expected, we showed that re-exposure to AI in the metastatic setting induced circulating mutation detection in a significant fraction of the patients. Our present findings point out the low interest in *ESR1* circulating mutation detection during the adjuvant setting, even for patients that will relapse.

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Funding: None

Disclosure: All authors have declared no conflicts of interest.

191P Pathological proliferation score to predict genomic risk categories in early stage breast cancer

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Background: Five of the 16 cancer-related genes used to calculate the Recurrence score (RS) are proliferative genes. Appropriate utilization of an expensive test is important especially in areas of limited resources. A relatively inexpensive 'Pathological Proliferative score' (PrS) of a tumor may help group patients in risk categories correlating with the RS.

Methods: We retrospectively studied 205 patients with Lymph node negative, hormone receptor (HR) positive, HER2 negative status (ODX candidates) between1990-2015 treated across three rural community oncology practices. Proliferation score was calculated by combining tumor grade, visual mitotic score and Ki67 immunostaining (on a scale of 1-3, lowest score of 3; highest score of 9). Log-rank test was used for survival analysis.

Results: PrS correlated with ODX risk recurrence ($p < 0.001$, Fischer's Exact test) [Table]. PrS predicted FFP ($p = 0.014$) at 10 years with PrS (3-4) 96%±2%, PrS (5-7) 91%±5% and PrS > (7-9) 75%±1%. It did not predict PFS($p = 0.77$), OS($p = 0.84$). Type of adjuvant treatment or none did not affect Low Prs(3-4) 10 yr PFS ($p = 0.18$ and OS ($p = 0.33$). Int/High PrS (5-9) showed benefit with adjuvant hormonal therapy compared to none at 10-year OS ($p = <0.001$), PFS ($p = 0.002$) and FFP ($p = 0.003$).

Table: 191P Correlation of ODX with PrS

	Proliferative Score (n = 190)			
	3 – 4 (n = 119)	5 – 6 (n = 37)	7 – 9 (n = 40)	p-value*
Genomic Risk				<0.001
Low	41 (87%)	11 (58%)	2 (11%)	
Intermedium	6 (13%)	7 (37%)	1 (5%)	
High	0 (0%)	1 (5%)	16 (84%)	
Unknown	72	18	21	
Genomic Risk				<0.001
Low	41 (87%)	11 (58%)	2 (11%)	
Intermedium/High	6 (13%)	8 (42%)	17 (89%)	
Unknown	72	18	21	

*p-value based on Fisher's Exact test

The 10 yr OS (p = 0.75), PFS (0.76) and FFP (p = 0.88) was not influenced by addition of adjuvant chemotherapy.

Conclusions: PrS which may represent an inexpensive screening approach to identify patients with a low ODX RS that have excellent outcomes despite the type of adjuvant treatment. ODX testing is unlikely to re-categorize them. Higher (5-9) PrS was not predictive of chemotherapy benefit, unlike high ODX. Lack of standardization of Ki67 staining, retrospective nature of the study while important should be tested in an expanded and prospective setting.

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Disclosure: All authors have declared no conflicts of interest.

192P Population sizes of patients (pts) with node negative (N0), HR+, HER2− primary breast cancer (BC), using standard and TAILORx 21-gene recurrence score (RS) cut-off values (COV)

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Background: Whether to use adjuvant chemotherapy (CT) is a crucial decision for pts with HR+, HER2− primary BC. The 21-gene Recurrence Score® (RS) assay is validated to predict adjuvant CT benefit and risk of recurrence, using standard RS COV of < 18, 18-30, and ≥31. Of ∼59K N0/N1 pts from two real-world registries, those with RS < 18 (>50% of total) largely treated without CT had favorable 5-y outcomes. The prospective TAILORx and PlanB clinical trials showed excellent 5-y outcomes for RS < 11 and RS ≤ 11 subgroups, respectively, treated without CT. The AJCC now recommends use of RS < 11 to down-stage to 1A. The capacity to generalize regional study outcomes globally requires first that RS subgroup sizes are geographically consistent. Here, we analyze RS subgroup sizes across geographical regions using standard and TAILORx COV.

Methods: Pts with N0, HR+, HER− primary BC and RS results from 2004 to April 2017 were included (data from Genomic Health). Subgroup sizes were determined for RS < 11, 11-17, 18-25, 26-30, and ≥31 in the US, Germany, the UK, France, and the rest of the world (RoW).

Results: Of 609,247 unique RS records analyzed, 513,035 were from the US, 29,248 from EU countries, and 66,964 from RoW. The relative population sizes of RS subgroups were highly consistent across geographical regions. Deviations in percentages for each RS range were within ±3% (Table). Across all regions, >50% of pts had RS < 18.

Conclusions: Our analysis revealed highly consistent RS subgroup classifications across geographic regions, mirroring observations from registry studies, suggesting that tumor biology as characterized by RS results does not vary by geography. Our findings therefore support the generalizability of outcomes-study results using standard or custom COV across geographic regions.

Legal entity responsible for the study: Jens-Uwe Blohmer

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193P Oncotype DX score, menopausal status and body mass index

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Background: The Oncotype DX assay uses expression of 21 genes to predict the risk of distant disease recurrence in patients with oestrogen receptor positive Her2 negative breast cancer. It has been demonstrated that increased intra-tumoural inflammation is associated with higher Oncotype score. An inflammatory milieu within the breast is associated with more aggressive histological cancer subtypes, and also with obesity, which is recognised as a risk factor for breast cancer. The association between obesity and breast cancer is higher in post-menopausal than pre-menopausal women. Therefore this study aimed to investigate whether there is a correlation between Oncotype score, menopausal status and obesity.

Methods: All patients with Oncotype assays performed between 2008 and 2016 in several centres in Ireland were identified. Data was retrospectively collected on weight, body mass index (BMI), menopausal status and Oncotype scores, including oestrogen (ER) and progesterone (PR) scores. Statistical analysis assessed correlation between Oncotype scores and these factors.

Results: Analysis was performed on 269 patients from a single centre with early stage breast cancer. Median age was 53.4 years and the majority of patients (58%) were post-menopausal at diagnosis. Patients who had a BMI less than 25 (normal weight) had significantly lower Oncotype score than those with BMI greater than 25 (overweight/obese) (p < 0.05). The Oncotype ER and PR scores were similar in normal weight and overweight patients, as were tumour size and grade. Post-menopausal patients had higher Oncotype scores than pre-menopausal patients (p < 0.001), with higher ER scores (p < 0.001) and lower PR scores (p < 0.001). On multivariate analysis, menopausal status remained significant as a predictor of Oncotype score. Complete analysis of an additional 600 patients will be performed.

Conclusions: Oncotype score is higher in overweight patients with early stage node-negative breast cancer. This difference appears to be independent of ER and PR scores and correlates with menopausal status. This retrospective study is the first to suggest that the body mass index and menopausal status of patients with early stage breast cancer may influence the Oncotype DX recurrence score and analysis of a further cohort of patients is ongoing.

Legal entity responsible for the study: Seamus O'Reilly

Funding: None

Disclosure: All authors have declared no conflicts of interest.

Table: 192P

	US (N = 513035)		UK (N = 10154)		Germany (N = 14856)		France (N = 4238)		RoW (N = 66964)		All regions (N = 609247)	
RS group	n	%	n	%	n	%	n	%	n	%	n	%
<11	109396	21	1775	17	2714	18	818	19	12989	19	127692	21
11-17	178070	35	3171	31	5295	36	1426	34	23499	35	211461	35
18-25	135783	26	2844	28	4207	28	1185	28	18622	28	162641	27
26-30	35512	7	848	8	1161	8	393	9	5000	7	42914	7
≥31	54274	11	1516	15	1479	10	416	10	6854	10	64539	11

194P Comparisons of tumor-infiltrating lymphocytes and 21-gene recurrence score in ER-positive/HER2-negative breast cancer

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Background: Recent meta-analysis showed that tumors with high tumor-infiltrating lymphocyte (TIL) have a higher probability of pathologic complete response even in Luminal/HER2-negative breast cancer. Also, the 21-gene recurrence score (RS) predicts the clinical benefit of chemotherapy for ER-positive/HER2-negative women. We compared two markers in those cancer.

Methods: In ER-positive/HER2-negative patients treated with primary surgery, the RS (Oncotype DX® Breast Cancer Assay; Genomic Health, Inc., USA) was obtained. We evaluated TIL in H&E slides of surgical specimens by standardized methodology proposed by the international TIL-working group. In 198 women, the percentage of stromal TIL was successfully assessed. In accordance with the recent meta-analysis, the degree of TILs were categorized as high ($>=$60%), intermediate (11-59%), and low ($<=$10%).

Results: Ninety-seven (49.0%), 88 (44.4%), and 13 patients (6.6%) had low, intermediate, and high TILs, respectively. There is a significant but weak correlation between continuous RS and continuous TIL (Pearson's R = 0.201, P = 0.004). The average of continuous RS was significantly highest in the high TIL tumors (17.8±10.7 in low TIL, 19.4±8.7 in intermediate TIL, and 26.2±8.2 in high TIL; P = 0.014). Whereas the average of continuous TILs was compared according to categorized RS, it was significantly higher in the intermediate RS or the high RS tumors (15.4±13.2 in low RS, 26.6±13.6 in intermediate RS, and 19.8±19.2 in high RS; P < 0.001). When we compared categorized RS and TIL, we found that the rates of the high TIL-tumors was significantly higher in the intermediate RS or the high RS (1.0% for low RS tumors, 12.5% for intermediate RS tumors, and 10.0% for high RS tumors; P = 0.007).

Conclusions: We found that tumors with high TIL tend to have a higher RS in ER-positive/HER2-negative breast cancer. We also noted that the rate of high-TIL tumors was significantly higher in the intermediate-RS tumors as well as in the high-RS tumors. Clinically, our findings suggest that TIL count might be referred in decision-making of chemotherapy in the intermediate RS-patients.

Table: 194P

	Low or Intermediate TIL	High TIL	P-vlaue
Low RS (N = 98)	97 (99%)	1 (1%)	0.007
Intermediate RS (N = 80)	70 (88%)	10 (12%)	
High RS (N = 20)	18 (90%)	2 (10%)	

Legal entity responsible for the study: N/A

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Disclosure: All authors have declared no conflicts of interest.

195P The 70-gene signature in node positive breast cancer: 10-year follow-up of the observational RASTER study

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Background: In early stage breast cancer patients, with axillary lymph node metastasis, the 70-gene signature, MammaPrint® (MP) identifies patients with a High or Low Risk of distant breast cancer (BC) recurrence. For MP Low Risk (G(enomic)-low) in patients with up to 3 positive lymph nodes (N1-3), the MINDACT trial (Cardoso, NEJM 2016) showed that it might be safe to forgo adjuvant chemotherapy. Here we evaluated the prognostic value of MP at 10 years follow-up in patients with lymph node positive early stage BC.

Methods: Between 2004 and 2006 812 women with early stage BC participated in the observational RASTER trial (Bueno de Mesquita, Lancet Oncol, 2007). 181 patients were node positive and not included in the primary analysis, 176 of them gave consent for future research. On 164 tumor samples (FFPE) MP was performed retrospectively. Survival data was collected and samples were allocated to clinical high (C-high) or C-low risk as used in MINDACT. Patients with over 3 axillary lymph node metastases (N4+) were all considered C-high. 10-year distant-recurrence-free-interval (DRFI) was compared between subgroups based on the MP and clinical assessment.

Results: In 3 patients the clinical assesment could not be determined. Over 95% of patients received chemotherapy, 82.9% (136/164) of tumors were ER-positive and 18.3% (30/164) of patients had N4+. MP identified 47% (n = 77/164) as Low Risk, including 16,9% (13/77) with N4+. 10-year DRFI in patients N1-3 and G-Low or G-High was 94.9% and 80.7% respectively (HR 4.7; 95%CI 1.3-16.2). With the clinical assessment 13.7% (n = 22/161) were low risk, only one was diagnosed with distant BC recurrence. 10-years DRFI was 94.4% in C-low and 85.8% in C-high (HR 3.7 95%CI 0.5-28.5). In N4+ 10-years DRFI was 69.7%. Combining the clinical assessment with MP risk assessment in patients N1-3 the 10-years DRFI in clinical high risk patients was 95.2% for G-Low (n = 44) and 79.6% for G-High (n = 65) (HR 4.83 95%CI 1.1-21.4).

Conclusions: We again confirm the prognostic value of Mammaprintin BC patients with axillary lymph node involvement after 10 years follow up. In N1-3 patients with clinical high risk, MP can identify a subgroup with excellent prognosis after standard adjuvant systemic therapy.

Legal entity responsible for the study: S. Linn

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Disclosure: All authors have declared no conflicts of interest.

196P Higher expression of estrogen response genes in the primary tumor is associated with a greater risk for late recurrence in patients with ER+/HER2-breast cancer

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Background: In patients with ER+ breast cancer, 50% of recurrences occur > 5 years after diagnosis (*i.e.* late recurrence). Clinical trials report contradicting results on the effect of extended endocrine therapy > 5 years to reduce late recurrence risk. Using publically available breast cancer gene expression profiles, we aimed to gain insight into the biology that increases the risk for late recurrences.

Methods: Gene expression profiles of primary ER+/HER2- tumors of breast cancer patients were collected with disease-free survival (DFS) data, defined as time of diagnosis to local recurrence or distant metastasis. We defined (i) a group containing all patients (n = 2,231), (ii) a group that received 5 years of endocrine therapy only (n = 591), and (iii) a group that received no systemic therapy (n = 497). For each group, genes were ranked on their association with DFS as determined by multivariate Cox regression with age, tumor size, grade, lymph node status, and therapy as covariates. Gene set enrichment analysis (GSEA) was performed on these gene lists with the Hallmark collection from the Molecular Signatures Database. Within each group, associations with early recurrence were studied in all patients with censoring at 5 years if no event occurred < 5 years after diagnosis (set I). To study associations with late recurrence, a second set was defined that contained only patients with a follow-up ≥ 5 years and no event < 5 years after diagnosis (set II).

Results: Within all patients and the group that received 5 years of endocrine treatment only, higher expression of genes belonging to the Hallmark 'estrogen response late' was associated with longer DFS in set I and shorter DFS in set II. This Hallmark contains estrogen responsive genes identified in estradiol treated ER+ breast cancer cell lines. However, in patients who received no systemic treatment, higher expression of these genes was associated with shorter DFS in both set I and II.

Conclusions: Higher expression of estrogen response genes is associated with a greater risk for late recurrence in patients with ER+/HER2- breast cancer. Potentially, patients with ER+ tumors with high expression of these genes might benefit most from extended endocrine therapy.

Legal entity responsible for the study: R.S.N. Fehrmann

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Disclosure: All authors have declared no conflicts of interest.

197P Understanding BRCA1 and BRCA2 mutated breast cancer cases in Romania: First report on founder mutations in Romanians

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Background: First systematic analysis of BRCA 1(B1) or BRCA2(B2) mutations in high-risk Romanian breast cancer patients (pts) aiming at defining founder mutations.

Methods: This prospective study evaluated the germline B1/B2 mutations in 250 high-risk breast cancer pts tested between 02.2015-12.2016 at IOCN. Inclusion criteria selected pts diagnosed with triple negative breast cancer under the age of 50, or having conventional family history criteria. All pts signed an informed consent. B1/B2 testing was performed using an AmpliSeq-based sequencing analysis, on the Ion Torrent Personal Genome Machine at RCFG. Pathogenic mutations were validated using Sanger technology. MLPA was performed for all pts.

Results: Of the 250 pts with breast cancer, 44 (17.6%) carried pathogenic mutations, 29 pts (11.6%) in B1 and 15 (6%)in B2, while 18 patients (7.2%) carried a Variant of Uncertain Significance (VUS). Patient features analysis confirmed the prevalence of younger age, higher grade, hormone receptor negative and Her2 negative status among mutated patients (data not shown). Out of the 16 distinct deleterious mutations identified, 7 (43.75%) occurred in B1 and 9 (56.25%) in B2. The founder mutations identified in B1 gene were: c.5329_5330insC (c.5266dupC) 11 pts (37.93%), c.3607C>T 9 pts (31.03%) and c.181T>G 4 pts (13.79%). Other B1 mutations where c.1687C>T 2 pts (6.89%), and c.4218delG (3.44%), c.212 + 1G>T (3.44%), c.68_69delAG (3.44%) in one patient respectively. For B2 gene, c.9371A>T (46.66%) was identified as founder mutation (7 pts, 46.66%). Other mutations were found each in one patient (6.66%): c.1528G>T, c.4022C>G, c.7007G>A, c.8695C>T, c.9253delA, c.8680C>T, c.8755-1G>A, c.8695C>T. Of the founder mutations identified, two (c.3607C>T and c.9371A>T) have not been previously identified as founder mutations in any Eastern European country.

Conclusions: This prospective study presents the first extensive results of germline B1/B2 mutations in Romanian high-risk breast cancer pts. Our results indicate that at least four recurrent B1/B2 mutations qualify as founder mutations; two being newly identified as carrying a founder effect. ClinicalTrials.gov Identifier: NCT02317120.

Clinical trial identification: NCT02317120

Legal entity responsible for the study: Alexandru Eniu

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Disclosure: A. Eniu: Research support: AstraZeneca, Roche, Novartis, Celltrion. All other authors have declared no conflicts of interest.

198P The prevalence of CD146 expression in breast cancer subtypes and its relation to outcome

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Background: CD146 has several putative (patho)physiological roles in breast cancer. The most prominent is its involvement in the induction of epithelial-to-mesenchymal transition, which might have an effect on cancer phenotype and aggressiveness. Here, we investigated the prevalence of CD146 expression and its prognostic role in breast cancer subtypes.

Methods: In total, 1,025 breast cancer patients were available for this retrospective study. From all patients, formalin-fixed paraffin-embedded primary breast cancer tissue was collected and embedded in tissue microarrays, which were stained for CD146. CD146 expression was defined as > 1% of the tumor cells showing CD146 membrane staining. Clinical data were available from all patients (median follow up 118 months, range 4-120). For subtype analysis the Pearson chi-square test was used and the Cox proportional hazards model for survival analyses. Only patients who were lymph node negative and did not receive (neo)adjuvant systemic treatment were included in the survival analyses (n = 551).

Results: 113 (11%) out of 1,025 tumors showed CD146 expression. Of these, 43% of the tumors had > 50% of the tumor cells showing CD146 membrane staining. From the molecular subtypes, CD146 positive tumors are often of the triple negative subtype (76 out of 119 (64%), $p < 0.001$) and histologically of the medullary type (11 out of 23 (48%), $p < 0.001$). In univariable analysis, CD146 was a prognostic factor for both poor metastasis-free survival (MFS) and overall survival (OS) (respectively HR 1.65, 95% CI 1.02-2.66, $p = 0.041$ and HR 1.66, 95% CI 1.03-2.69, $p = 0.037$). When correcting for the traditional prognostic factors (including age, tumor size and grade, ER, PR and HER2) in multivariable analysis, CD146 was not an independent prognostic factor for MFS and OS (respectively HR 1.63, 95% CI 0.93-2.87, $p = 0.088$ and HR 1.46, 95% CI 0.82-2.61, $p = 0.197$).

Conclusions: CD146 protein expression is present in 11% of the primary breast cancer tumors and is most prevalent in the triple negative and medullary subtypes. CD146 is a prognostic factor for MFS and OS in breast cancer patients, but it is not independent of the traditional prognostic factors. Its potential impact on outcome to systemic treatment such as endocrine therapy, remains to be established.

Legal entity responsible for the study: Erasmus University Medical Center

Funding: None

Disclosure: All authors have declared no conflicts of interest.

199P Neutrophil-to-lymphocyte and lymphocyte-to-monocyte ratios in breast cancer

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Background: Immunity plays a pivotal role in cancer progression and prognosis. A high neutrophil-to-lymphocite ratio (NLR) or a low lymphocyte-to-monocyte ratio (LMR) are respectively associated with systemic inflammation and immune suppression and have been associated with a poor outcome. Aim of this study is to further investigate the interaction between the immune system and breast cancer (BC) through the NLR and LMR.

Methods: This retrospective study analyzed a consecutive cohort of 657 patients (pts) with a diagnosis of pT1 BC, without restrictions regarding lymph node status (T1BC), or metastatic BC (MBC) treated between 2004 and 2017 at the Department of Oncology of Udine (Italy). Differences in terms of NLR and LMR among the two cohorts and between clinico-pathological characteristics in the T1BC subgroup were explored through the Kruskal-Wallis test. The prognostic impact in terms of OS in the T1BC population was investigated through uni- and multivariate Cox regression.

Results: Both NLR and LMR were significantly different between the T1BC and the MBC cohorts. In particular, pts with T1BC had a higher median LMR (3.9 vs 2.9; $P = 0.0001$) and lower NLR (2 vs 2.7; $P = 0.0001$). After stratification according to molecular profile, T1BC and MBC cohorts of Luminal B-like subtype were significantly different in terms of both LMR (4.2 vs 3; $P = 0.0001$) and NLR (2 vs 2.5; $P = 0.0001$). In triple negative subtype, the difference between TB1C and MBC was observed for NLR (1.9 vs 3.2; $P = 0.0272$) only. On the other hand, no differences between TB1C and MBC were highlighted for the other subtypes. When focusing on the clinico-pathological characteristics of the T1BC cohort, LMR was associated with progesterone receptor (PR) expression ($P = 0.0261$) and marginally with the estrogen receptor (ER) expression, while NLR with tumor diameter ($P = 0.0240$) and marginally with grading. Furthermore, among T1BC pts, NLR had no prognostic impact in terms of OS, while LMR was associated with a better outcome also when corrected for ER, PR and HER2 status (HR 0.44, 95%CI 0.28 - 0.71, $P = 0.001$).

Conclusions: These results suggest a role for systemic inflammation and immune-suppression in breast cancer, especially in the triple negative and luminal B-like subtypes.

Legal entity responsible for the study: University of Udine

Funding: None

Disclosure: All authors have declared no conflicts of interest.

200P Vitamin D as a prognostic factor in triple negative early breast cancer

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Background: Triple negative breast cancer remains without a target therapy. Interventions that could improve pathological complete response (pCR) rates are required. Metabolits of vitamin D could be involved in chemotherapy response.

Methods: A series of 147 patients with early or locally advanced triple negative breast cancers was retrospectively analyzed from 2007 to 2016. Patients from 2015 to 2016 period were supplemented with vitamin D and calcium (880UI/1000mg). Analysis of clinicopathological, immune variables and vitamin D pathway were correlated to pCR.

Results: Median age was 53, median tumor size 30mm, 48% had nodal involvement, and median ki67 expression was of 70%. Androgen receptor was expressed in 28% of tumors analyzed, EGFR in 89%, CK5/6 in 63%. Mean stromal T lymphocytes infiltrates (sTILS) was of 28%, mean PDL1 expression of 128, mean 53BP1 expression of 125, and mean VDRnuc expression of 132. pCR rate was of 40%, and within patients with vitamin D supplementation was 64% (16/25). Only VDRnuc expression was associated with pCR ($p = 0.047$) in the univariate and multivariate analysis. Patients with high expression of VDRnuc in tumor had no evidence of relapse ($p = 0.024$), with similar curves than those who achieve pCR ($p = 0.000$).

Conclusions: VDRnuc expression is a strong predictive ($p = 0.047$ with pCR) and prognostic ($p = 0.024$ with relapse) in triple negative breast cancer. Role of supplementation needs to be tested if it could improve VDRnuc levels; whereas in our series patients with supplementation had better pCR rates.

Legal entity responsible for the study: Hospital Universitari Arnau de Vilanova de Lleida Institut de Recerca Biomèdica

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Disclosure: All authors have declared no conflicts of interest.

201P CDK12: New breast and ovarian cancer predisposition gene in Tatar population?

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Background: The development of hereditary ovarian and breast cancer (OC/BC) is often caused by genetic defects in the DNA repair system. However, the diagnostics in most medical centers of Russia includes PCR-based identification only the eight common mutations in BRCA1/2 for the Slavic population. Previously we established that patients of the Tatar population with OC/BC did not possess most of Slavic mutation and a significant part of the predisposition is due to other mutations in the genes of the homologous recombination (HR) system. The aim of this work is the analysis of the germline mutations in the HR genes.

Methods: The DNA from 175 blood samples from patients of the Volga District with hereditary OC/BC were analyzed by targeted NGS (Roche NimbleGen, Illumina MiSeq), the comparison groups included blood samples from patients of Slavic origin.

Results: 62% of the detected pathogenic mutations were presented in the *BRCA1/2* genes. The remaining mutations were found in other genes of the reparation system (HGMD Professional 2017.1 database). An unexpected finding was the detection of a germline splicing mutation *c.1047-2A>G* in *CDK12* gene (Chr17(GRCh37):37627130A>G, NM_016507.3) in patients of Tatar origin (Table).

Mutation *c.1047-2A>G* is more common in patients with OC/BC in comparison with healthy controls (7/224 vs 0/316, p = 0.002, OR = 21.49, CI 95% = 1.22–377.25).

Table: 201P *CDK12 c.1047-2A>G* frequency distribution

Subjects origin	BC or OC	Healthy controls
Tatar from Volga District	6/94 (6.4%)	0/32 (0%)
Non-Tatar from Volga District	1/81 (1.2%)	–
Slavic from Moscow	0/49 (0%)	0/284 (0%)
ExAC NFE	–	29/64446 (0.045%)
1000G	–	2/5006 (0.039%)

Conclusions: Gene *CDK12* is one of the most frequently altered genes in serous ovarian cancers, but significance of *CDK12* germline mutations in hereditary cancers remains to be defined. Its role in carcinogenesis of OC was established recently and *CDK12* was not included in most NGS panels of HR genes. Our study demonstrates that *CDK12* may be novel candidate gene for OC/BC genetic predisposition. Notably, frequency of *CDK12 c.1047-2A>G* (6.4%) mutation is comparable with frequency of founder-mutation *BRCA1 5382insC* (7.4%), that indicates its possible founder role in Tatar population.

Legal entity responsible for the study: Tatarstan Cancer Center

Funding: Kazan (Volga Region) Federal University, Tatarstan Cancer Center

Disclosure: All authors have declared no conflicts of interest.

202P Prognostic value of master transcriptional regulators (MTRs) in early stage breast cancer

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Background: Multigene prognostic signatures (MGPS) enable identification of candidate patients (pts) for treatment de-escalation in early stage BC. However, currently available MGPS do not completely address clinical needs by adequately incorporating lymph node (LN)-positive pts and clinicopathological information (CPI). Here, we present OncoMasTR, a MGPS for determining the risk of distant recurrence (DR) in ER-positive, HER2-negative BC pts with up to 3 involved LNs. OncoMasTR, discovered via a novel network analysis methodology that determines upstream MTRs has been mechanistically verified and offers improved prognostic value compared to existing MGPS. OncoMasTR has been further trained to include LN-positive pts and CPI.

Methods: Two independent sample sets: 225 pts from Malmö University Hospital and 106 pts from Skåne University Hospital were used for training, cross-validation and refinement of OncoMasTR. RNA extracted from 225 archived tissues was analysed by RT-qPCR and expression levels of the MTRs were determined by normalising against the expression levels of reference genes. The strongest prognostic combinations of MTRs were identified using statistical models of all possible combinations of MTRs. Clinical performance of the models with the best cross-validated performance in the training data were further evaluated in the 106 independent samples.

Results: OncoMasTR classifies up to 72% of LN0 pts and 60% of LN0-3 pts as low risk, with only 4.9% and 5.5% recurrence rate within the respective groups. When incorporating selected CPI, its prognostic performance further improved to a concordance index of above 0.8. Results showed that the OncoMasTR Molecular score (mS) alone adds statistically significant information to the CPI, and the Combined score (cS) also adds statistically significant information to the mS.

Conclusions: OncoMasTR offers significant prognostic information to the standard CPI and addresses the unmet clinical need of LN-positive pts. The binary output of OncoMasTR, giving no ambiguous intermediate group helps eliminate uncertainty in the formation of the final treatment decision. OncoMasTR is ready for large-scale clinical validation and, subsequently, clinical translation.

Legal entity responsible for the study: OncoMark Ltd

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203P Survival outcomes of all patients treated with breast carcinosarcoma at a UK specialist cancer centre over a 10 year period (2004–2014)

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Background: Carcinosarcoma of the breast is a rare and aggressive type of breast cancer presenting as a high grade tumour with lower rates of both lymph node metastasis and oestrogen and progesterone receptor (ER/PR) expression when compared to the more common types of breast cancer, carrying a less favourable prognosis. We present the clinical and pathological findings and outcomes of a series of patients diagnosed and treated for breast carcinosarcoma at a UK specialist cancer centre.

Methods: We conducted a retrospective review of data for all patients diagnosed with breast carcinosarcoma between October 2004 and October 2014 at the Clatterbridge Cancer Centre NHS Foundation Trust.

Results: Nine patients were diagnosed in the 10-year period, with a median age at diagnosis of 73 years (range 37-76 years). Seven patients (77.8%) were postmenopausal. Six patients (66.7%) presented with a palpable mass. T1, T2, and T3 were found in 1, 6 and 2 patients respectively. N0, N1, and N2 were found in 6, 2 and 1 patients respectively. All patients had G3 disease with a median diameter of 3cm (range 1.9-9.0 cm). Oestrogen receptor (ER) and progesterone receptor (PR) were both negative in 8 patients (88.9%). Whilst one patient had wide local excision, all the rest had mastectomy, of whom 4 had axillary nodal clearance and 4 had sentinel nodal biopsy. Five patients received adjuvant radiotherapy. Adjuvant chemotherapy was delivered to 5 patients (2 patients received neither treatments) and adjuvant hormone therapy was delivered to 2 patients (one of whom had a concurrent contralateral ER/PR positive tumour). Patients were followed up for a median period of 15 months (range 1-60 months). Median DFS is estimated to be 25 months and median OS is estimated to be 49 months (95% CI: 14-84 months). Two patients (22.2%) developed metastases with a DFS time of 13 and 14 months respectively, and both died within 5 months.

Conclusions: Within a 10 year period during which our specialist cancer centre were referred 16,500 new breast cancer patients, only 9 patients had carcinosarcoma. Prognosis following recurrence is poor within our limited cohort, in agreement with the published literature. In order for more meaningful analysis of survival outcomes for such a rare form of breast cancer, a multicentre collaborative approach is required.

Legal entity responsible for the study: Clatterbridge Cancer Centre

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204P ESR1, Ph-mTOR, CDK4/6 and PD-L1 expression as prognostic (and potentially druggable) drivers for pure invasive lobular breast carcinoma (ILC): Preliminary results of prognostic outliers according to a clinical-pathological model

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Background: The biological drivers of prognosis for pure ILC are not entirely clear. The aim of this analysis was to investigate the molecular and immune-related portrait of prognostic outliers to identify different patterns of expression associated with prognosis and potentially *druggable*.

Methods: Clinical-pathological multi-center data of resected early-stage pure ILC patients (pts) were correlated to disease-free and overall-survival (DFS/OS). A continuous score was derived according to multivariate Hazard Ratios, in order to derive a 3-class model (Poor/Intermediate/Good Prognosis). IHC (for Ph-mTOR, CDK6, PD-L1), FISH (for ESR1, Ph-mTOR, CDK4, PD-L1) and H&E evaluation (for stromal Tumor Infiltrating Lymphocytes, sTILs) were performed upon pts at Poor and Good Prognosis. Odds Ratio (OR) with 95% CIs for the risk of association with prognostic class of biomarkers was determined.

Results: Data from 457 pts were gathered (median age 57 years, median follow: 75 months). The 3-class cross-validated model significantly differentiated DFS and OS ($p < 0.0001$, prognostic accuracy: 0.65 and 0.71, respectively). Based on DFS, 154 and 20 pts with Good and Poor prognosis, respectively, were identified. The preliminary and exploratory analysis of the first 34 pts (Good/Poor 14/20) is reported (OR < 1: higher chance to be associated with Good prognosis; OR > 1 higher chance to be associated with Poor prognosis).

Table: 204P

Biomarker [Method]	OR	95% CIs
High sTILs [H&E]	0.22	0.01-5.8
Ph-mTOR deletion [FISH]	0.33	0.07-1.49
ESR1 gain [FISH]	0.53	0.09-3.18
PD-L1 positive [IHC]	0.67	0.08-5.4
CDK4 deletion [FISH]	1.22	0.1-15.1
PD-L1 gain [FISH]	1.25	0.19-8.2
Score 3+ CDK6 [IHC]	2.29	0.21-24.68
Score 3+ Ph-mTOR [IHC]	2.48	0.61-10.05
ESR1 deletion [FISH]	2.75	0.27-23.04
CDK4 gain [FISH]	3.18	0.15-66.36

Conclusions: Despite unpowered, these preliminary data suggest that Poor and Good prognosis are potentially associated to differential expression of a cluster of biomarkers: ESR1 deletion, CDK4 gain, CDK6 and ph-mTOR over-expression versus high sTILs, PD-L1 positive, ESR1 gain and ph-mTOR deletion, respectively.

Legal entity responsible for the study: University of Verona

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205P The pregnancy and fertility (PREFER) study: A prospective cohort study on fertility-preserving (FP) strategies in young early breast cancer (EBC) patients (pts)

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Background: Premature ovarian failure and subsequent infertility are possible long-term side effects of chemotherapy (CT) in young EBC pts. Limited data are available on the number of pts who consider FP strategies and on the reasons for refusal of these procedures. To address the significant challenges related to fertility issues, the PREFER study was developed as a national comprehensive program aiming to optimize care and improve knowledge around this topic.

Methods: This is a prospective cohort study ongoing across several Italian centers affiliated to the GIM (Gruppo Italiano Mammella) study group. Oncologists offer the available FP strategies to young EBC pts undergoing (neo)adjuvant CT: oocyte cryopreservation (OC), ovarian tissue cryopreservation (OTC) and LHRH analogue (LHRHa) during CT. Eligible pts are premenopausal, $\leq$ 45 years, no previously exposed to CT and/or radiotherapy. Primary objective is to obtain data about preferences and choices of young EBC pts on the FP strategies. Secondary objectives are to evaluate the success and safety of FP strategies, hormonal changes during CT and survival outcomes. The present analysis reports preliminary results of the study including pts enrolled at the coordinating center from November 2012 to May 2017.

Results: A total of 131 EBC pts were enrolled; median age was 38.9 years (24.8-45.34). Nine pts (6.87%) refused all FP options. Reasons for refusal were no interest in fertility preservation (5 pts), previous pregnancy (3 pts), no interest in having children (1 pts). LHRHa was accepted by 120 pts (91.6%) and 27 pts (20.6%) accepted gynecologic counseling. Among these pts, 10 (7.6%) accepted OC or OTC. Main reason for refusal of cryopreservation procedures was fear of delaying cancer treatment (3 pts). No complications were observed among women who underwent OC or OTC. Median number of mature oocytes yielded and cryopreserved was 8.5 (4-13). A patient had a spontaneous pregnancy following adjuvant treatment.

Conclusions: Despite the great importance of fertility issues in young EBC pts, a minority of them (7.6%) require to access cryopreservation procedures. This is crucial information from a public health perspective and for resource allocation.

Clinical trial identification: NCT02895165

Legal entity responsible for the study: IRCCS AOU San Martino IST, Genoa Italy

Funding: AIRC - Associazione Italiana per la Ricerca sul Cancro (IG 2013 No14272).

Disclosure: All authors have declared no conflicts of interest.

206P Incidence of permanent alopecia following adjuvant chemotherapy in women with early stage breast cancer

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Background: Alopecia is one of the most distressing toxicities of adjuvant chemotherapy for patients with breast cancer. Historically, oncologists have reassured patients (pts) that chemotherapy-induced alopecia is temporary, and followed by full hair recovery. More recently there have been troubling reports of permanent alopecia following adjuvant taxanes (Tax). We studied the incidence of long-term hair loss in patients treated on adjuvant trials in our institution. Patients who were enrolled on clinical trials involving Tax (D-Docetaxel, P-Paclitaxel) and/or Anthracyclines (A) were included.

Methods: We conducted a telephone interview survey of pts who had completed adjuvant or neo adjuvant A and/or T chemotherapy on clinical trials more than one year before. Ongoing alopecia was graded as 0 (full hair recovery), 1 (mild hair loss) or 2(severe/total). The study was approved by the hospital audit committee.

Results: We studied 295 pts who has been treated on 12 studies. Drug exposure: D-260 pts (D nonA-185, D+A-75); A-nonTax-12 pts; A+P 23 pts. The overall incidence of alopecia was 15% (11% grade 1 and 4% grade 2). For all D the incidence was 15% (12% Grade 1 and 3% Grade 2). For D+A-24% (19% Grade 1 and 5% Grade 2). For D non A the incidence was 13% (8% grade 1 and 5% grade 2). For A non T 8% (Grade 2-8%). For PA-13% (4% grade 1 and 9% grade 2). For patients receiving D non-A regimens, there were two levels of D exposure, 300mg/m^2 (90 pts) or 450 mg/m^2 (95 pts). The incidence of alopecia was significantly D dose dependent: D300- 7% (all grade 1) and D 450-19% (14% grade 1, 5% grade 2) (p=.02 chi$^{2)}$. Among the higher dose D group, the companion drug choices carboplatin for HER2 positive, (55 pts) or cyclophosphamide (40 pts) were associated with similar incidences of permanent alopecia (22% v 16%).

Conclusions: Permanent alopecia is a common complication of adjuvant chemotherapy. The risk appears to be highest in regimens which contain A and D, but it is also seen in D non-A, AP and in A non-Tax. For patients receiving D non A, the risk is dose-dependent. Our set contains few P pts, and no pts undergoing low dose weekly P. Oncologists should warn all patients undergoing adjuvant therapy of the risk of permanent alopecia.

Legal entity responsible for the study: John Crown

Funding: None

Disclosure: All authors have declared no conflicts of interest.

207P Significant changes in dietary intake and physical activity after breast cancer diagnosis in a Chinese breast cancer cohort study

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Background: The diagnosis of cancer can motivate survivors to modify lifestyles, typically involving diet and physical activity. Few data have reported pre- and post-diagnostic lifestyle habits in Chinese population.

Methods: In an on-going prospective cohort study which involved 1462 Chinese women with early-stage breast cancer, we evaluated dietary intake and lifestyle factors pre- and post- breast cancer diagnosis. Validated food frequency questionnaires were used to evaluate dietary intake. Leisure time physical activity was measured by a modified Chinese Baecke questionnaire. This report compared changes of dietary intake and physical activity between 12 months before and 18 months after diagnosis of breast cancer.

Results: Intake of whole grains, refined grains, fruits, vegetables, eggs, and nuts increased significantly post-diagnosis (Range, 54%-72% increase; $P < 0.001$, each; Table). Conversely, after diagnosis consumption of red meat, processed meat, poultry, dairy products, soy, sugar drinks, and coffee significantly decreased (Range, 32%-63% decrease; $P < 0.001$, each). The level of physical activity (MET-hour per week) post-diagnosis was significantly increased (median, 0.75 vs. 5.25; $P < 0.001$), with 58% of patients became more physically active. However, the proportion of women that met the WCRF/AICR Cancer Prevention recommendations about physical activity (10 MET-hour per week) was still low, only 21% women met at pre-diagnosis, increasing to 34% at post-diagnosis.

Table: 207P

Food group	Pre-diagnosis [Median (IQR), g/1000kcal/day]	Pre-diagnosis [Median (IQR), g/1000kcal/day]
Refined grains	269.9 (213.3-348.3)	319.6 (257.8-391.2)
Whole grains	3.6 (0-11.9)	7.4 (0.7-30.0)
Fruits	95.1 (54.3-137.8)	140.4 (92.0-193.6)
Vegetables	194.1 (136.8-263.2)	271.5 (197.3-359.8)
Eggs	8.3 (4.1-14.8)	10.1 (5.2-16.9)
Red meat	48.3 (29.1-72.7)	38.2 (20.3-62.0)
Processed meat	1.7 (0.3-4.8)	0.4 (0-2.4)
Poultry	20.4 (9.6-38.2)	1.1 (0-7.1)
Dairy products	15.4 (5.0-44.5)	5.7 (0.6-15.9)
Soy	28.1 (12.8-55.1)	23.3 (8.3-49.0)

*IQR, inter quartile range.

Conclusions: In this cohort study, Chinese breast cancer patients reported significant changes in dietary intake and increased physical activity level and a higher proportion met the WCRF/AICR Cancer Prevention recommendations after cancer diagnosis. These findings provided crucial information on lifestyle behaviors in Chinese breast cancer survivors, and provided information to healthcare professionals on survivors' health and quality of life.

Legal entity responsible for the study: The Chinese University of Hong Kong

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Disclosure: All authors have declared no conflicts of interest.

208P Prevention of cardiotoxicity in breast cancer patients: A randomized prospective study

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Background: Adjuvant anthracyclin chemotherapy (ANTC) and trastusumab are documented to prolong survival in breast cancer patients. However, these drugs are well known to induce Left Ventricular Systolic Dysfunction (LVSD). Multiple studies showed that acetyl choline-esterase inhibitor (ACEIs) and beta Blockers (BBs) can prevent LVSD.

Methods: One hundred and twenty six patients with M0 breast cancer patients to be treated with ANTC ± trastuzumab were randomized to an intervention group (group 1) (n = 63 patients) which received cardioprotective drugs; (ACEI;enalapril) and (BB;carvedilol) or to a control group which did not receive cardioprotective drugs (group 2) (n = 63 patients). To evaluate systolic and diastolic functions conventional echocardiography (Simpson method and M- mode) and cardiac magnetic resonance imaging (CMR) were performed at baseline, after 3 cycles and 6 cycles of ANCT, and after 1 year of follow-up. Cardioprotective drugs received: Both enalapril and carvedilol were started at least 24 hours before the first chemotherapy cycle.

Results: In the intervention group 58 patients had 3 cycles ANTC, 6 patients received 6 cycles ANTC, and 12 patients received trastuzumab. Whereas in the control group 47 patients had 3 cycles ANTC, 16 patients were given 6 cycles ANTC and 18 patients received trastusumab. After 3 ANTC cycles, LVEF did not change in group 1 (64.35% at baseline vs. 63.59%, p 0.2) but decreased by M- mode in the control group (64.84% at baseline vs. 63.42%, p 0.03) associated with statistically significant deterioration of diastolic function grades. At 1 year follow-up, while no change was observed in LVEF in group 1, there was decrease in LVEF by CMR in group 2 (65.78% at baseline, 61.48% at 1 year, p 0.048). No cases were detected with heart failure or with final EF < 45% in either group. Compared to controls, the intervention group had a statistically significant lower incidence of decrease EF ≥ 10% after finishing ANTC by CMR(1.9% vs. 12.5%, p 0.04).

Conclusions: Combined prophylaxis with ACEI (enalapril) and BB (carvedilol) may prevent LVSD in patients with non-metastatic breast cancer treated with anthracyclines containing chemotherapy ± trastuzumab. The clinical relevance of this strategy should be confirmed in larger randomized studies.

Legal entity responsible for the study: Academic Group

Funding: None

Disclosure: All authors have declared no conflicts of interest.

209P Quality-of-life results from a randomized, phase-II-study of the therapeutic cancer vaccine L-BLP25 (Stimuvax®) in the preoperative treatment of women with primary breast cancer (ABCSG-34)

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Background: In ABCSG-34, patients with HER2-negative breast cancer were randomized to preoperative standard of care therapy (SoC) with or without L-BLP25 (Stimuvax). This report describes the quality-of-life (QoL) results of the trial.

Methods: 400 patients were randomized to receive SoC with or without BLP25. Postmenopausal women with low-risk disease (ER +++/ ++, Ki67 <14%, G1/2) received 6 months of letrozole; premenopausal and postmenopausal patients with triple-negative, ER-/+/ ++, Ki67 ≥14%, or G3 tumors received 4 cycles of epirubicin/cyclophosphamide plus 4 cycles of docetaxel with or without L-BLP25. Primary end point results RCB and pCR rates were presented previously (SABCS 2016; Abstract Nr 850339). QoL was assessed with the EORTC QLQ-C30 and EORTC QLQ-BR 23 at baseline, before surgery, and up to 4 weeks thereafter. The objective was to evaluate differences of QoL in women treated with or without L-BLP25, as well as between the two regimens.

Results: 385 patients from 17 centers were included in the QoL analysis. There were no differences in QoL between patients receiving SoC only and those receiving additional L-BLP25. Impact on QoL was determined by the SoC therapy and by the timepoint of the assessment. Before surgery and 4 weeks thereafter patients receiving chemotherapy ± TL-BPL25 showed more impairment in the QoL scales role and social functioning, financial problems and body image than the patients receiving endocrine therapy ± TL-BPL25. Fatigue and hair loss were significantly more common in the chemotherapy than in the endocrine arm. At the time of surgery and thereafter, patients in both SoC arms had significantly negatively impacted QoL (physical, role, emotional, cognitive, social, sexual functioning, body image domains) as well as more fatigue, pain, dyspnoea, breast and arm symptoms. There were no differences in global health status between the arms at the different time points.

Conclusions: Addition of L-BLP25 (Stimuvax) to SoC in HER2-negative EBC patients does not impair QoL.

Legal entity responsible for the study: ABCSG

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Disclosure: All authors have declared no conflicts of interest.

210P Dedicated breast PET for predicting residual disease after breast cancer neoadjuvant chemotherapy

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Background: Diagnostic methods to evaluate the response to breast cancer neoadjuvant chemotherapy (NAC) have been established. Dedicated breast PET (DbPET) is a high-resolution molecular breast imaging method, and we investigated the ability of DbPET to predict the presence of residual primary tumors after NAC, compared with whole-body PET (WBPET).

Methods: Forty-five patients (47 tumors) underwent WBPET and ring-type DbPET after NAC, and tumors were completely resected between January 2016 and March 2017. The pathological response was classified as complete remission (ypT0), residual intraductal disease (ypTis), or residual invasive disease (ypT≥1). Standardized uptake value (SUV) and tumor-to-normal tissue ratio (TNR) were assessed.

Results: Twelve patients achieved ypT0 and 5 developed ypTis. DbPET detected all cases of ypTis, and WBPET detected only one case of ypTis. The sensitivity, specificity, and accuracy of WBPET for ypT≥is were 54.3%, 83.3%, and 61.7%, respectively, and those of DbPET were 77.1%, 83.3%, and 78.7%, respectively. In the ypT0/ypTis/ypT≥1 groups, the median WBPET-SUV, DbPET-SUV, and DbPET-TNR were 1.0/0.9/1.1, 1.7/1.8/2.2, and 1.0/1.6/1.7 (P = .134, .077, and .008), respectively (Table). Area under the curves of WBPET-SUV, DbPET-SUV, and DbPET-TNR for predicting ypT≥is were 0.610, 0.648, and 0.807, respectively.

Table: 210P Comparison of predicting indexes for predicting pathological response

Pathological response	WBPET-SUV		DbPET-SUV		DbPET-TNR	
	Median (IQR)	*p*	Median (IQR)	*p*	Median (IQR)	*p*
ypT≥1	1.1 (0.9-1.7)	.134	2.2 (1.5-3.9)	.077	1.7 (1.1-2.9)	.008
ypTis	0.9 (0.9-1.2)		1.8 (1.4-1.9)		1.6 (1.4-1.8)	
ypT0	1.0 (0.9-1.0)		1.7 (1.5-2.1)		1.0 (0.9-1.1)	

Conclusions: DbPET was superior to detect residual primary tumors, especially noninvasive carcinoma, after NAC than WBPET. TNR was expected as the better parameter of pathological evaluation than SUV.

Legal entity responsible for the study: N/A

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Disclosure: All authors have declared no conflicts of interest.

212TiP IMpassion031: A phase III study comparing neoadjuvant atezolizumab (atezo) vs placebo in combination with anthracycline/nab-paclitaxel (nab-pac)–based chemotherapy in early triple-negative breast cancer (eTNBC)

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Background: Atezo is an anti–programmed death-ligand 1 (PD-L1) monoclonal antibody that prevents PD-L1 from binding to PD-1 and B7.1 receptors, thereby restoring tumor-specific immunity. TNBC is characterized by PD-L1 expression on tumor-infiltrating immune cells (IC), a high mutation rate and high levels of tumor-infiltrating lymphocytes (TILs), suggesting a therapeutic opportunity for atezo. Atezo alone and in combination with nab-pac is well tolerated, with promising activity in metastatic TNBC, supporting its investigation in early-stage disease. IMpassion031, a global Phase III, double-blind, randomized, multicenter, placebo-controlled study, is being conducted to evaluate the efficacy and safety of neoadjuvant treatment with nab-pac → doxorubicin + cyclophosphamide and either atezo or placebo in invasive stage II/III eTNBC. The choice and sequence of chemotherapy is selected to maximize the opportunity to establish a robust immune response.

Trial design: Patients (pts) with previously untreated, central laboratory–confirmed invasive TNBC with primary tumor size > 2 cm and ECOG PS 0-1 are eligible. Exclusion criteria include history of invasive BC, stage IV disease, and prior immunotherapy or autoimmune disease. Approximately 204 pts will be randomized 1:1 to receive atezo (840 mg q2w) or placebo with nab-pac (125 mg/m^2 qw) for 12 weeks, followed by atezo (840 mg q2w) or placebo with doxorubicin (60 mg/m^2 q2w) + cyclophosphamide (600 mg/m^2 q2w) for 4 cycles before surgery. Pts will be unblinded post-surgery and pts in the atezo arm will continue to receive atezo (1200 mg q3w × 11 doses). Stratification factors include stage II vs III at diagnosis and PD-L1 expression (IC0 vs IC1/2/3). The primary endpoint is pathological CR (pCR); key secondary endpoints include pCR according to PD-L1 status, pt-reported outcomes, event-free survival and overall survival. Tumor samples will be taken at baseline, on treatment (optional), at surgery and post-recurrence and will be assessed for biomarkers associated with responses and immune escape.

Clinical trial identification: NCT number available on poster

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

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213TiP PIONEER- Pre-operative wIndOw study of letrozole plus PR agonist megestrol acetate versus letrozole aloNE in post-menopausal patients with ER-positive breast cancer

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Background: Recent preclinical findings have been published which provide new insights into the functional cross-talk between the estrogen receptor (ER) and the progesterone receptor (PR) in breast cancer (Mohammed et al., Nature, 2015). Addition of a PR agonist to anti-estrogens directly modifies ERa chromatin binding and the transcriptional response in breast cancer cells, and is anti-proliferative in vitro and in vivo. Megestrol Acetate (MA), an off-patent semi-synthetic derivative of progesterone, has been licensed for many years as a treatment for ER+ metastatic breast cancer. There is

also good evidence for the effectiveness of MA as a supportive therapy to ameliorate endocrine therapy-related hot flushes.

Trial design: PIONEER is a three-arm, open label, multi-centre randomised phase II pre-surgical window trial evaluating effects of 15 days of preoperative therapy with Letrozole (LET), or LET plus MA 40mg, or LET plus MA 160mg in postmenopausal women with newly diagnosed, ER+ HER2- invasive primary breast cancer. Patients are being recruited in Cambridge, with 5-6 other UK sites due to open in q3/4 2017.

Table: 213TiP 3-arm randomisation

Arm A	LET 2.5mg daily
Arm B	LET 2.5mg daily + MA 40mg daily
Arm C	LET 2.5mg daily + MA 160mg daily

The primary endpoint is % change in proliferation between baseline and day 15 tumour biopsies, measured by Ki67 immunohistochemical (IHC) assessment. Secondary endpoints include: expression of Aurora Kinase A, Caspase 3 and Androgen receptor/PR/EMT markers by IHC; and safety endpoints. Exploratory endpoints include: transcription factor mapping (ChIP-seq) on paired fresh-frozen tumour samples. Patients are randomised in a 1: 1.5: 1.5 ratio for arms A: B: C. Based on results from previous clinical trials, a mean 66% reduction in Ki67 is anticipated for LET alone (arm A), and a 77.5% reduction for combination arms B and C, based on preclinical data. A recruitment total of 189 patients is required. Pioneer will help determine if there is value in conducting a follow-on adjuvant study to investigate the longer term benefit of combining an aromatase inhibitor with MA, and if so, at what dose (40mg vs. 160mg).

Clinical trial identification: EudraCT Number: 2016-003752-79 MHRA/REC number: v2.0 5th June 2017

Legal entity responsible for the study: Cambridge University Hospitals NHS Foundation Trust and the University of Cambridge

Funding: Anticancer Fund

Disclosure: All authors have declared no conflicts of interest.

214TiP VENTANA (SOLTI-1501): Antiproliferative effect of the addition of oral metronomic vinorelbine to endocrine therapy in luminal/HER2-negative early breast cancer: A window of opportunity trial

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Background: The cornerstone of luminal breast tumors treatment both in early and advanced settings is endocrine therapy (ET). Although extended adjuvant ET has demonstrated benefit, a significant percentage of patients relapse. In previous studies, the combination of ET with CDK4/6 inhibitors has shown unprecedented efficacy suggesting that inhibition of the cell cycle in combination with ET is a strategy to keep exploring. The efficacy and safety of metronomic VNB have been confirmed in preclinical and clinical studies and it is now considered a multi-mechanisms of action therapy that could offer advantages when combined with other drugs. VENTANA study is a "window-of-opportunity" trial designed to explore whether, similarly to CDK4/6 inhibitors, oral metronomic VNB in combination with endocrine therapy induces a superior antiproliferative effect than ET alone. We hypothesize that the synergistic biological effect of the combined treatment could be an alternative to CDK4/6 inhibitors in the treatment of luminal breast cancer patients.

Trial design: Pts are randomized (1:1:1) to receive LET 2.5mg daily, oral VNB 50mg 3 days a week, or the combination. After 3 weeks of treatment, pts undergo surgery. Pre- and post-treatment (surgical) samples will be analyzed for gene expression. The primary objective is to test if oral metronomic VNB and LET induce a superior antiproliferative effect than either drug alone in pts with early BC defined as Luminal by PAM50. This will be evaluated by the expression of 11 proliferative genes contained in the PAM50 subtype predictor (BIRC5, CCNB1, CDC20, CDCA1, CEP55, KNTC2, MKI67, PTTG1, RRM2, TYMS and UBE2C) as surrogate signature biomarker of its anticancer activity. In addition, 560 BC-related gene signatures will also be analyzed. Enrollment started in July 2016 in 10 sites across Spain. To date, 47 patients have been included. We expect to report full study results by Spring 2018.

Clinical trial identification: NCT02802748

Legal entity responsible for the study: SOLTI Breast Cancer Research Group

Funding: Pierre Fabre

Disclosure: All authors have declared no conflicts of interest.

215TiP PALLAS: PALbociclib CoLlaborative adjuvant study: A randomized phase 3 trial of palbociclib with standard adjuvant endocrine therapy versus standard adjuvant endocrine therapy alone for HR+/HER2-early breast cancer

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Background: Cell cycle inhibition is a proven target for novel cancer therapeutics. Palbociclib (P) is an orally active inhibitor of CDK4/6, and arrests the cell cycle at the G1-S transition. P in combination with endocrine therapy (ET) has demonstrated efficacy in phase II and III randomized trials for patients with newly diagnosed and recurrent hormone receptor positive/HER2 negative (HR+/HER2-) metastatic breast cancer (MBC), and is approved in these settings. Given confirmed benefits of P and ET for MBC, the PALLAS study was designed to determine if the addition of P to adjuvant ET improves outcomes over ET alone in HR+/HER2- early breast cancer.

Trial design: PALLAS is an international open-label phase III trial randomizing (1:1) patients (pts) to 2 years of P (125 mg daily, 21 days on 7 days off in a 28-day cycle) combined with at least 5 years of provider choice ET (AI, tamoxifen, +/- LHRH agonist), versus ET alone. The primary objective of the study is to compare invasive disease-free survival (iDFS) for the combination of P and ET, versus ET alone. Secondary objectives include comparison of iDFS excluding cancer of non-breast origin, DRFS, LRRFS, OS, as well as safety. The principal objective of the translational investigations is to determine the predictive or prognostic utility of defined genomic subgroups with respect to iDFS and OS. Additional objectives include evaluation of cfDNA and tissue biomarkers predictive of benefit or resistance, pharmacogenomics, adherence, and patient-reported QOL. Eligible pts are pre- or post-menopausal women or men with stage II-III, HR+/HER2- breast cancer. Patients may have already initiated ET, but must be randomized within 12 months of diagnosis and 6 months of initiation of adjuvant ET. Trial sample size is 4600 pts and stage IIA pts will be capped at a total accrual of 1000 pts. Interim analyses for safety, futility/efficacy and sample size re-estimation are planned. PALLAS opened in 9/2015 and accrual is ongoing. Contact information: emayer@partners.org.

Clinical trial identification: US: IND Nr.(FDA): 126003 clinicaltrials.gov NCT02513394 FDA approval 27 May 2015 Non-US (clinicaltrialsregister.eu dates): EudraCT Number: 2014-005181-30 Sponsor Protocol Number: AFT-05/ABCSG-42/BIG_14-03 Start Date: 2015-07-09

Legal entity responsible for the study: Alliance Foundation Trials (AFT) LLC for US, ABCSG GmbH for participating countries outside of the US

Funding: Pfizer

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216TiP OlympiA: A randomized phase III trial of olaparib as adjuvant therapy in patients with high-risk HER2-negative breast cancer (BC) and a germline BRCA1/2 mutation (gBRCAm)

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Background: In a Phase II study (NCT00494234), treatment with olaparib, a potent, orally available PARP inhibitor, exerted antitumor activity in patients (pts) with advanced BC harboring a gBRCAm. In a randomized phase III trial, olaparib significantly improved PFS compared to chemotherapy (CT) for patients with HER2-negative gBRCAm advanced BC (OlympiAD, NCT02000622, ASCO 2017). OlympiA (NCT02032823) is a phase III trial of olaparib as adjuvant therapy for pts with high risk gBRCAm HER2-negative BC who have completed local treatment and (neo)-adjuvant CT.

Trial design: OlympiA is a double-blind trial in which high risk HER2-negative pts are randomized (1:1) to receive treatment with olaparib (300 mg tablets bid [2 x 150 mg]) or placebo for 12 months. Eligible pts must have completed local treatment and at least 6 cycles of (neo)-adjuvant containing anthracyclines and/or taxanes. Pts with triple negative BC (TNBC) must have $\geq$pT2 or $\geq$pN1 in the adjuvant and non-pCR in the neoadjuvant setting. Pts with hormone receptor (HR) positive BC must have $\geq$4 positive lymph nodes in the adjuvant and non-pCR and CPS&EG score $\geq$3 in the neoadjuvant setting. Pts must also harbor a deleterious gBRCAm. Stratification factors include hormone receptor status, prior neoadjuvant versus adjuvant CT, and whether pts have received platinum therapy for current BC. The primary objective is invasive disease-free survival (IDFS). Efficacy assessments will be made by mammograms/breast MRI scans annually for 10 years, beginning 6 months from randomization, and by medical history/physical examination from randomization every 3 months for 2 years, then every 6 months for a further 3 years and annually thereafter. Secondary objectives include overall survival, distant DFS, incidence of new non-BCs, HRQoL, safety and tolerability. The primary IDFS analysis will be performed after 330 IDFS events using a stratified log-rank test. Patient enrolment began in April 2014 and is currently ongoing. The target number for randomization is 1500 patients across ~500 sites and ~25 countries worldwide. Support: U10CA12027,-69651,-37377,-69974,-180868,-180822, -189867; AstraZeneca.

Clinical trial identification: NCT00494234

Legal entity responsible for the study: AstraZeneca

Funding: AstraZeneca and NRG Oncology

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ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

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BREAST CANCER, LOCALLY ADVANCED

217O A gene signature of chemo-immunization to predict outcome in patients with triple negative breast cancer treated with anthracycline-based neoadjuvant chemotherapy

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Background: The extent of tumor-infiltrating lymphocytes (TILs) in the residual disease after anthracycline-based neoadjuvant chemotherapy (NACT) is associated with a better prognosis, in patients with triple-negative breast cancer (TNBC). We aimed to develop a genomic signature from pre-treatment samples to predict the extent of TILs after NACT, and then to test its prognostic value on survival.

Methods: Using 99 pre-treatment samples (training set), we generated a four-gene signature that predicts post-NACT TILs using the LASSO technique. Prognostic value of the signature on survival was first assessed on the training set ($n = 99$) and then evaluated on an independent validation set including 185 patients with TNBC treated with NACT.

Results: A four-gene signature combining the expression levels of HLF, CXCL13, SULT1E1, and GBP1 predicted the extent of lymphocytic infiltration after NACT. In a multivariate analysis performed on the training set, a one-unit increase in the signature value was associated with distant-relapse free survival (DRFS) (HR: 0.28, 95%CI: 0.13-0.63, $p = 0.0018$). For the validation dataset, the four-gene signature was significantly associated with DRFS in the entire set (HR: 0.26, 95%CI: 0.11-0.59, $p = 0.0012$) and in the subset of patients with residual disease (HR: 0.23, 95%CI: 0.10-0.55, $p = 0.0008$).

Conclusions: We developed a four-gene signature of immune-activation, which predicts outcome in patients treated with NACT for TNBC.

Legal entity responsible for the study: Carmen Criscitiello

Funding: Transcan-2011, Operation Parrain Chercheurs, Odyssea, Fondation Dassault.

Disclosure: All authors have declared no conflicts of interest.

218P Prognostic estimates of Ki-67 percentage drop after neoadjuvant chemotherapy (NAC) in luminal B (lumB) and triple negative breast cancer (TNBC)

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Background: Pathologic complete response (pCR) and residual cancer burden (RCB) after NAC are validated prognostic markers in BC. We assessed the impact of adding Ki-67% drop (baseline biopsy - surgery) to distant metastasis relapse-free survival (dRFS) models containing CP factors plus post-treatment stage (MDACC CPS score), estrogen receptor status and tumor grade (MDACC CPS+EG score).

Methods: Records from 341 patients (pts) with lumB/HER2 neg (baseline Ki67 >20%) or TNBC who received NAC from 2008 to 2015 at our hospital were reviewed. Uni- and multivariate Cox models were constructed and concordance-index (c-index) calculated.

Results: Pts: median age 47 years (24-83), 60% lumB and 40% TNBC, 62% stage 2, 38% stage 3. pCR: 12% lumB, 32% TNBC ($p < 0.01$). Median Ki-67% drop: 24% lumB, 5% TNBC ($p < 0.01$), without differences by NAC regimen. dRFS at 5 year-median follow-up was 75% in lumB (CI95% 67-83) vs 62% in TNBC (CI95% 53-74, $p < 0.01$); 90% in RCB 0/1 (CI95% 81-97) vs 74% in RCB 2/3 (CI95% 65-83, $p < 0.01$). As compared to pts with RCB 0/1, those with RCB 2/3 plus Ki-67% drop $>= 20\%$ (best cut-off in univariate model) had similar dRFS at 5 years (90%, CI95% 81-100, $p = 0.48$), irrespective of molecular group. Enrichment for Ki-67 $>=$20% drop in lumB (60%) vs TNBC (30%, $p < 0.01$) was observed. Both CPS and CPS+EG scores were validated as independent prognostic factors in univariate dRFS models (c-index of 0.70 and 0.78, respectively). The addition of Ki-67% drop ($< 20\%$ vs $>= 20\%$) to CPS and CPS+EG scores in multivariable models significantly improved their performance (c-index of 0.74 and 0.81, respectively). Ki-67 $>= 20\%$ drop associates with 70-80% reduction in distant relapse risk (HR 0.27 and 0.16 in CPS and CPS+EG models, respectively, $p < 0.05$).

Conclusions: Our data support the addition of Ki-67% drop after NAC in lumB and TNBC to existing dRFS online outcome calculators. In the context of RCB 2/3, Ki-67 $>= 20\%$ drop is mainly seen in lumB/HER neg tumors. Importantly, Ki-67 $< 20\%$ drop identifies a high-risk population that may be eligible to clinical trials with novel therapeutic interventions in the adjuvant setting.

Legal entity responsible for the study: Vall d'Hebron University Hospital

Funding: Vall d'Hebron Institute of Oncology

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219P Immune function and response to neoadjuvant chemotherapy in hormone receptor positive, HER2-negative breast cancer

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Background: Gene expression (GE) signatures and Tumor Infiltrating Lymphocyte (TILs) enumeration have shown promise as predictors of response to neoadjuvant chemotherapy in Hormone Receptor negative (HR-) and HER2+, but not in HR+/HER2- breast cancer (BC). This study aimed to explore their predictive value in HR+/HER2- BC, based on previous work from our group on the association of immune function and chemosensitivity in advanced HR+ BC.

Methods: The PROMIX phase 2 trial enrolled patients with locally advanced HER2-BC to receive six cycles of epirubicin and docetaxel, plus bevacizumab during cycles 3-6. Patients underwent tumor biopsies at baseline and after cycle 2 for GE profiling using DNA microarrays and TIL enumeration according to standard guidelines. Since pathologic complete remission (pCR) is relatively rare in HR+ BC, we also associated an immune gene module score (IMS) and TIL counts with the non-dichotomous variable of decrease in tumor size.

Results: Of the 150 enrolled patients, $n = 113$ were HR+. For $n = 71$, both TIL and GE data were available at baseline, while for $n = 78$ and $n = 49$ patients longitudinal TIL and GE data at baseline and cycle 2 were available, respectively. At baseline, on both univariate (OR = 2.29, $P = 0.037$) and multivariate analysis (OR = 2.35, $P = 0.044$) IMS was associated with pCR, while its association with tumor shrinkage was only apparent on univariate ($P = 0.047$) and not multivariate analysis ($P = 0.061$). TIL infiltration >50% ($n = 9$) was associated with neither pCR (OR = 1.812, $P = 0.61$) nor tumor shrinkage ($P = 0.99$). However, decreases in TIL counts in cycle 2 compared with baseline were associated with lesser decreases in tumor size ($P = 0.043$ for univariate and $P = 0.044$ for multivariate analysis).

Conclusions: Baseline immune function as assessed by GE analysis, but not TIL enumeration, and a preserved abundance of TILs after chemotherapy were predictive for chemosensitivity at the neoadjuvant setting in patients with HR+, HER2- BC.

Clinical trial identification: NCT00957125

Legal entity responsible for the study: Karolinska University Hospital

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220P Safe resection margins in breast-conserving surgery

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Background: Our first research concerning resection margins in breast-conserving surgery (BCS) for breast cancer patients (BCP) was performed in 2003-2006. In the group of BCP where after positive margins we performed mastectomy (0%) and in the group where the negative margins were achieved immediately (1.27%) the incidence of local recurrences was lower comparing to the group that had re-resections (4.76%) or the group without microscopic control of margins (8.16%). We tried to understand the causes of local recurrences after BCS, and develop recommendations on achieving safe resection margins.

Methods: To clarify the possibility of cancer spreading to the side of regional lymph nodes we were injecting a solution of aqueous methylene in four points around a tumor in 30 minutes before surgery and subsequently we were studying cuts made at the distance up to 5 cm from the tumor margin. In 12% of cases we identified tumor elements in cuts located at a distance of more than 3 cm. In this study we included 996 BCP of I-III stages who had BCS at the National Cancer Institute in 2008-2015. The main group consisted of 379 BCP who had an additional removal of tissues towards the axillary area as a monoblock during the BCS (with additional histological control as mentioned above). 617 BCP in the control group had standard BCS. The average age of BCP was $50.6 \pm 1{,}1$ in the main group, and $49{,}8 \pm 0{,}9$ in the control group ($p > 0.05$). Median follow-up was 142 weeks.

Results: Achieving negative margins at the area of possible metastasis significantly reduces local recurrence rates, especially in a stage II (5.34%) and III (3.35%) BCP. The incidence of distant metastases (diagnosed in 93 (9.34%) cases) was significantly lower in the main group – 21 (5.54%) comparing to the control group – 72 (11.67%), both in general and in each stage ($p < 0.05$). Time of distant metastases occurrence was slightly lower in the control group – $84{,}7 \pm 8{,}9$ weeks, comparing to the main group – $101{,}3 \pm 9{,}5$ weeks ($p > 0.05$).

Conclusions: BCS with the additional removal of tissues towards the axillary area and lymph nodes dissection as a monoblock is reasonable and significantly reduces local and distant metastases rates. However, more long-term research in this area is urgently needed, especially in terms of benefit in survival.

Clinical trial identification: The study is approved by the Commission on issues of ethics of the National Cancer Institute (Protocol No. 7 of 08.04.2010) and the Commission on issues of ethics of the Bogomolets National Medical University (Protocol No. 71 of 10.04.2013).

Legal entity responsible for the study: Bogomolets National Medical University, National Cancer Institute

Funding: None

Disclosure: All authors have declared no conflicts of interest.

221P A clinically applicable model to predict risk of relapse in patients treated for locally advanced breast cancer: Potential utilization in future clinical trials

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Background: Despite advances in cancer treatment, over 25% of patients (pts) with locally advanced breast cancer (LABC) relapse during first 5 years after treatment. The primary objective was to construct a prediction tool for risk of relapse (RR) in pts with LABC after neoadjuvant therapy (NAT).

Methods: This was single center, retrospective study of 546 pts with LABC who received NAT at the Ottawa Hospital Cancer Center between 2005 and 2015. Median follow-up was 49 months. The following data collected: demographics, tumor size, nodal and receptor status, grade, HER-2, stage, treatment and clinical outcomes. Primary endpoints were local and/or distant recurrence rate and time to relapse during the first 5 years. A prediction tool was devised based on the Cox regression model.

Results: Over 60 variables were included in primary analysis. Cox regression proportional hazards model analysis resulted in only 5 factors with significant influence on risk of relapse during first 5 years of follow up. Risk factors and their risk prediction value are: 1) residual disease (yes- 4; no-0), (HR = 4.25; p-value<0.001), 2) lymph nodes status (positive-3; negative-0), (HR = 2.27; p-value=0.006), 3) Inflammatory histology (yes-2; no-0), (HR = 1.90; p-value=0.003) 4) estrogen receptors status (positive-2; negative-0), (HR = 2.07; p-value=0.001), 5) Adjuvant radiotherapy (yes-0; no-1), (HR = 1.76; p-value=0.036). When these factors are combined the following Relapse Prediction (RP) Score can be constructed. According to this simple RP score, patients can be classified into to three groups (RP score – 0-5; 6-7; 8-12). RR was 7 times higher in patients with RP Score 8-12 vs patients with score 0-5 (p-value<0.001). Internal validation of proposed model was performed. ROC analysis of the proposed model revealed a sensitivity of 75%.

Conclusions: Patients with LABC represent a heterogeneous group with diverse risk of disease recurrence that can be predicted. Patients with high risk may require additional treatment and/or more active follow-up strategies and this simple model may be used to design unique studies in LABC based on RP score. We intend to further validate this model on a larger multi center/provincial population.

Legal entity responsible for the study: Olexiy Aseyev

Funding: None

Disclosure: All authors have declared no conflicts of interest.

222P Role of radiotherapy and its impact on survival of male breast cancer: Experience from a tertiary cancer center

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Background: Male breast Cancer (MBC) is a rare disease accounting for about 1% of all malignancies in men and 1% of all breast cancers. These patients(pts) are managed like female breast cancers. There is limited literature available defining the role of radiotherapy(RT) in management of MBC. We conducted a retrospective analysis to study the impact of adjuvant RT on outcome of MBC pts treated at our centre.

Methods: Review of MBC pts presenting to our centre from 2005 to 2015 was done. All underwent pre-treatment evaluation in a combined tumor clinic comprising radiation, surgical and medical oncologist. Most pts were treated with surgery followed by adjuvant therapy and kept on regular follow up. Overall survival (OS) was defined as time from pathologic diagnosis to last follow up or death. Disease free survival (DFS) was defined as time from diagnosis to first relapse.

Results: 96 pts of MBC were identified. Median age was 58 years (range 28-83). Clinical stage I, II, III and IV were 8, 27, 39 and 22 respectively. Of 66 pts with known receptor status, 83% were ER positive, 82% PR positive, 20% Her-2/neu positive and 7.5% triple negative. 69 pts underwent modified radical mastectomy or wide local excision. 54% were pathologically node positive. Adjuvant RT was delivered to 34% pts at 1.8-2 Gy per fraction to a median dose of 50 Gy (range 45-60 Gy). Radiation field comprised of chest wall with (75%) or without regional nodes (25%). Median follow up was 24 months (range 9-132). 16 pts had relapse out of which 4 had local and 13 had distant (most common site bone) metastases after a median duration of 19 mnths. 2 yr estimated DFS for the entire cohort was 79.2% and 2 yr OS was 85.7%. The 2 yr DFS in pts undergoing surgery was 86.4% vs 29.2% in those who did not($p = 0.001$). Pts who received adjuvant RT had better 2 yr DFS (92.4% vs 52.9%, $p = 0.002$). Adjuvant chemotherapy did not significantly affect the 2 yr DFS (93.1% vs 73%, $p = 0.123$).

Conclusions: MBC mostly present in advance stages at our centre and harbor HR positive disease with low HER-2 overexpression. Adjuvant RT provided a statistically significant improvement in outcome. Longer follow up of these cohort of pts is required for accurate evaluation of role of RT in MBC.

Legal entity responsible for the study: All India Institute of Medical Sciences

Funding: None

Disclosure: All authors have declared no conflicts of interest.

223P Early characteristics of breast neoplasms on contrast-enhanced ultrasonography and its clinical value

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Background: To investigate the characteristics of breast neoplasms on contrast-enhanced ultrasonography and its clinical value.

Methods: 225 female patients with breast masses unable to be diagnosed by conventional ultrasonography were examined with contrast-enhanced ultrasonography (CEUS). Their ages range were 12 to 85 years, the mean age was 45.8 ± 17.6 years. 225 cases were investigated. For cases of multiple lesions, performed which was the highest classification level of BI-RADS; for the lesions of the same level, performed the largest lesion. The characteristics of these masses on CEUS were analyzed and compared with the results of pathology examination. The contrast agent(UCA) was SonoVue (Bracco, Italy).

Results: 91 cases were malignant and 134 cases were benign. The 91 malignacies displayed: irregular shapes were 80.2%(73/91), tortuous, massive or penetrating vessels were 86.8% (79/91), heterogeneous distribution of contrast enhancement were 83.5% (76/91), perfusion defect of contrast signals were 89.0% (81/91), local retention of contrast signals were 93.4% (85/91), rapidly entering and exporting from the lesions were 65.9% (60/91). Significant differences of above CEUS characteristics were found between the benign and malignant breast lesions ($P < 0.05$), The two most important features were perfusion defects and local retention of the contrast signals, with the sensitivity and specificity attained to 89.0% and 91.8%, and 93.4% and 92.5%, respectively. Poorly defined boundaries of the 91 malignacies were 64.8%(59/91), and the specificity was 47.8%. The malignant cases had enlarged maximum diameter on CEUS compared to pre-contrast ($P < 0.05$).

Conclusions: The typical features of breast cancers on CEUS were irregular shapes, tortuous, massive or penetrating vessels, heterogeneous distribution of contrast enhancement, with perfusion defect or local retention of contrast signals, rapidly entering and exporting from the lesions, enlarged maximum diameter of the lesions on CEUS compared to pre-contrast. It is valuable for CEUS in the diagnosis and differential diagnosis of breast neoplasms clinically.

Clinical trial identification: From 2011 to 2015

Legal entity responsible for the study: The Center of Interventional Ultrasound Diagnosis in Nanjing Region

Funding: None

Disclosure: All authors have declared no conflicts of interest.

224P Synchronous and metachronous breast cancer in Ukraine

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Background: This study aims to evaluate the current state of multiple primary malignant neoplasms (MPMN) in Ukraine and develop decision criteria for type of surgical treatment for these patients.

Methods: The study included 2,032 patients who received special treatment at the Department of Breast Tumours at the National Cancer Institute in 2008-2015. Among them there were 195 MPMN patients where 107 (54.9%) presented synchronous cancer (SC) and 88 (45.1%) presented metachronous cancer (MC). The average age of patients was 46.6, and the number of postmenopausal women was 63.1%. Among SC patients there were 60 (56.1%) with only breast localizations and 47 (43.9%) with combination of breast and other localizations (gynaecological etc.), and among MC there were 41 (46.6%) with only breast localizations and 47 (53.4%) with combination of breast and other localizations. All the patients were evaluated in terms of aggressiveness of the disease, survival rates, as well as risk factors and treatment options.

Results: The clinical course of the disease (CCD) in MPMN patients was worse in SC patients comparing to MC patients (p=0.00162). A more aggressive CCD was observed in patients exposed to radiation from the Chernobyl accident ($p = 0.000798$). There was no influence on CCD of such factors as primary localization, type of special treatment, age and type of settlement. However, the impact of type of surgery was statistically proven, i.e. CCD in patients who underwent mastectomy was worse comparing to patients who underwent breast-conserving surgery (p=0.00048). Plastic and reconstructive surgery in SC patients was statistically proven as reasonable increasing overall survival by 29% (p=0.015). There was an influence of local recurrences on the overall survival in SC patients reducing it by 71% (p=0.033), however, there was no influence in MC patients.

Conclusions: The MPMN patients have to get an improved attentive management and treatment. Medical and surgical oncologists should concern all the risk factors that have influence on CCD in these patients and provide the best option of management. The research in this area of oncology is open and this is crucial to continue researches for better outcome of these patients.

Clinical trial identification: The study is approved by the Commission on issues of ethics of the National Cancer Institute (Protocol No. 7 of 08.04.2010) and the Commission on issues of ethics of the Bogomolets National Medical University (Protocol No. 71 of 10.04.2013).

Legal entity responsible for the study: Bogomolets National Medical University, National Cancer Institute

Funding: None

Disclosure: All authors have declared no conflicts of interest.

225P Clinical outcomes of single versus double hormone receptor positive breast cancer patients treated with neoadjuvant chemotherapy

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Background: This study aimed to evaluate and compare tumor response rates and survival outcomes between single and double hormone receptor (HR) positive (+) [Estrogen Receptor (ER+)/Progesterone Receptor (PR) negative (-) or ER-/PR+ versus ER+/PR+] breast cancer (BC) patients with any HER2 status treated with neoadjuvant chemotherapy at a single institution.

Methods: A retrospective review was conducted using the Sunnybrook "Biomatrix" database to identify eligible patients. A multivariable logistic regression analysis (MLR) was performed to assess the association between HR status (single or double HR+) and pathologic complete response (pCR) rates at surgery. A Kaplan-Meier method was used to estimate Disease Free Survival (DFS) and a log-rank test was used to compare DFS between 3 subgroups of patients: single or double HR+ and HR negative patients.

Results: Three hundred and four BC patients were identified and included in the analysis with a median follow up of 43.3 months (Q1-Q3: 28.7-61.1) and a mean age of 49.7 years (Standard deviation 10.9). Forty seven percent (47/101), 31% (11/36) and 14% (24/167) of patients with HR negative, single HR+ and double HR+ disease achieved a pCR respectively (X^2 test <0.0001). In a MLR analysis, HR status and HER2 status were associated with pCR rates. Compared to HR negative patients, patients with double HR+ disease were less likely to achieve pCR (Odd ratio (OR):0.14, 95%CI 0.06-0.31, $p<0.0001$) while single HR+ patients did not differ (OR:0.51, 95%CI 0.19-1.4). The association between HR+ status (single versus double HR+) and pCR rates compared to HR negative patients remained the same in subgroup analyses of HER2+ and HER2 negative patients separately. No difference in survival (DFS) was seen between the 3 subgroups of patients: HR negative, single and double HR+ patients.

Conclusions: BC patients with single HR+ disease behave differently than double HR+ patients in terms of likelihood of achieving pCR after neoadjuvant chemotherapy and do not differ from HR negative patients. This difference does not translate into a difference in DFS. Prospective studies are needed to validate these findings before considering different treatment strategies for these 2 subgroups of HR+ BC patients.

Legal entity responsible for the study: Jacques Raphael

Funding: None

Disclosure: All authors have declared no conflicts of interest.

226P The correlation between toll-like receptor genes polymorphisms, tumor microenvironment characteristics and the effectiveness of preoperative chemotherapy for locally advanced breast cancer

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Background: Toll-like receptor (TLR) activation may be an important event in tumor cell immune evasion. TLR2 and TLR4 gene polymorphisms correlate with increased susceptibility to cancer development, response to conventional chemotherapy in various organs.

Methods: Treatment results of 62 patients with breast cancer stages T1-3N0-3M0 treated with neoadjuvant chemotherapy were evaluated. The level of the post-treatment CD4+, CD8+, FOP3+ tumor-infiltrating immune cells and Ki-67 positive cells were studied. The polymorphisms of TLR4 (C399T) and TLR2 (G753A) genes were investigated using a PCR restriction fragment length polymorphism method. Statistica10.0 software was used to perform analysis of variance.

Results: ER+ and PR± expressing tumors were identified in 69.3% of patients, ER and PR negative tumors - in 30.6%. Pathological complete response (pCR) was identified in 14.6%. Genotype CC of TLR4 (C399T) gene was detected in 87%, whereas genotype CT - in 9.6% and genotype TT - in 3.4% of patients. Genotype GG of TLR2 (G753A) gene was detected in 88.7%, genotype GA - in 11.3% of patients. A correlation was found between polymorphisms of TLR2 (G753A) and axillary lymph nodes involvement. In carriers of GA genotype of TLR2 gene (G753A) we found more frequent axillary LN metastases ($\chi 2=5.75$; $p = 0.01$). A direct correlation was identified between level of Ki-67 and the level of regulatory FOXP3 cells in carriers of GA genotype of TLR2 gene($r = 0.96$; $p = 0.008$). There appears to be a relationship between TLR4 gene and levels of CD4 + (p=0.01) and CD8 + (p=0.02) as well as an association between TLR4 (C399T) gene and residual cancer burden (RCB) ($p = 0.04$). In carriers of TT genotype of TLR4 gene the level of CD4+ cells was significantly lower ($p = 0.03$). In carriers of CC genotype of TLR4 (C399T) gene we found a direct correlation between the level of CD8+ cells and Ki- 67 in the residual tumor ($r = 0.38$, $p = 0.01$). Higher level of CD4+ is associated with lower RCB in carriers of CC genotype of TLR4 (C399T) gene ($r = 0.3$, $p < 0.05$).

Conclusions: Preliminary results of the study indicate that further elucidation of the role of the TLRs in breast cancer development is promising.

Legal entity responsible for the study: National Cancer Institute

Funding: National cancer institute

Disclosure: All authors have declared no conflicts of interest.

227P Triple negative breast cancer: 10-year survival update of the applied treatment strategy in Kuwait

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Background: Triple negative breast cancer (TNBC) is recognized as a distinct clinical and biological entity of poor outcome for almost two decades, yet its treatment strategy still needs to be better specified. The study aim is to update the 10-year survival data of our TNBC patients and to find its association with different applied treatment modalities.

Methods: We updated 10-year survival data of 359 women diagnosed with TNBC between 1999 and 2009 in Kuwait Cancer Control Center (KCCC). The overall survival (OS), disease free survival (DFS), distant metastasis free survival (DMFS) and locoregional free survival (LRFS) were estimated using Kaplan Meier method. Survival was correlated with different prognostic factors and treatment modalities. Statistical significance was calculated using the log-rank test and defined as $p < 0.05$. Cox regression was used for Multivariate analysis.

Results: TNBC represented 12% of breast cancer in Kuwait with a median age of 48 years. The stage distribution was as follow: stage I, II, III, IV in 15%, 43%, 35% and 7%

of patients respectively. Regarding surgery, 33% had Conservative surgery; 67% had mastectomy and 82% had axillary clearance. Chemotherapy was neoadjuvant in 25%, adjuvant in 56% and palliative in 5% of patients. Two-thirds of patients (67%) received adjuvant radiotherapy. After a median follow-up of 108 months, the 10-year OS, DFS, DMFS and LRFS were 66%, 59%, 72% and 77% respectively. The 10-year OS was 92%, 80%, 49% and 0% for Stage I,II,III and IV respectively ($p = 0.0000$). OS was significantly worse with the presence of lymphovascular invasion (LVI; $p = 0.003$). OS was not significantly affected by age, grade or treatment modality. In multivariate analysis, the clinical stage and LVI were still significant (P = 0.0000 and 0.04 respectively).

Conclusions: In absence of biological biomarkers, the clinical stage and LVI seems to be the only significant prognostic factors for survival of TNBC patients in our study population. Timing of chemotherapy as well as the extent of surgery do not seem to affect the TNBC patients' outcome.

Legal entity responsible for the study: KCCC

Funding: None

Disclosure: All authors have declared no conflicts of interest.

228P A decade of HER2-targeted therapy in older patients with invasive breast cancer at Institut Curie

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Background: Around 40% and 20% of breast cancers (BC) occur in women aged ≥ 65 and ≥ 75 years respectively. Although HER2-targeted therapy has profoundly improved the management of HER2+ BC, literature is short of data for frail and elderly patients reflecting the poor representation of older patients in registration trials.

Methods: We conducted a retrospective analysis of any stage HER2+ BC patients aged ≥ 65 years treated with a HER2-targeted therapy at Institut Curie between 2000 and 2012 to assess treatment feasibility. Baseline data were extracted from the institution database and patients' files were reviewed for treatment compliance and safety profile.

Results: From 2000 to 2012, 261 and 76 patients received anti-HER2 treatment in adjuvant and metastatic setting respectively. In adjuvant setting (age distribution 65-69/70-74/$\geq$75: 109/85/67; median follow-up 65 months), the median duration of trastuzumab treatment was 12 months with an 80% completion rate (defined as $>$ 9 months of treatment) decreasing significantly ≥ 75 years (70%). Grade ≥ 3 cardiac toxicity occurred in 9.6% of patients, was reversible in 72% of cases, and multivariate analysis identified the following risk factors for cardiac events: history of thromboembolic disease, valvulopathy and performance status (PS) ≥ 2 [OR 6.3 (95% CI: 1.4-27.7), 25.6 (4-162.8) and 18.2 (1.1-304.3) respectively], but not age. In metastatic setting (age distribution 65-74/$\geq$ 75: 41/35; median follow-up 27 months), median duration of HER2-targeted therapy was 22.8 months (0-109.2), with no impact of age. Trastuzumab and lapatinib (alone or in combination) were mostly prescribed, pertuzumab and T-DM1 representing $<$ 15% of cases depending on treatment line. Multivariate analysis identified the following factors for mortality: PS ≥ 2, history of thromboembolic disease [OR 3 (95% CI: 1.1-8.1) and 3.3 (0.7-16.3) respectively], but not age.

Conclusions: HER2-targeted therapy seems feasible in ≥ 65 yrs patients in both adjuvant and metastatic setting. Cardiac toxicity occurs in 10-15% but is reversible in most cases. Chronological age does not seem to affect duration of anti-HER2 treatment nor cardiac toxicity.

Legal entity responsible for the study: Geiss Romain

Funding: None

Disclosure: All authors have declared no conflicts of interest.

229P Dedicated breast PET to predict pathological complete response after neoadjuvant chemotherapy for breast cancer

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Background: Reports indicate that whole-body (WB) ^{18}F-fluorodeoxyglucose (FDG) PET can predict a pathological complete response (pCR) after neoadjuvant chemotherapy (NAC). New dedicated breast PET (DBPET) can generate high-resolution images and thus might be able to predict pCR after NAC. The present study aimed to determine whether or not DbPET can predict the effects of NAC for breast cancer more effectively than WBPET.

Methods: The clinical responses of 35 consecutive patients with breast cancer (T1–4, N0–1, M0) who underwent NAC between January 2016 and January 2017 were assessed using WBPET and DBPET. We assessed maximum standardized uptake values (SUVmax), before (pre-SUVmax) and after (post-SUVmax) NAC and rates of change in SUVmax (ΔSUVmax) before and after NAC. Relationships between these parameters and pathological responses (pCR) were assessed using each modality. We created receiver operating characteristics curves (ROC), calculated areas under them (AUC) for both WBPET and DBPET images and predicted pCR.

Results: Twelve of 35 patients achieved pCR. The median pre-SUVmax, post-SUVmax and ΔSUVmax among the 35 patients determined using WBPET and DBPET were 6.8 and 18.0, 1.7 and 3.1, and 78.2 and 77.6, respectively. Uptake of ^{18}F-FDG was indistinguishable from background in WBPET, but confirmed in DBPET after NAC in three of 23 patients with non-pCR disease. The median pre-SUVmax of WBPET and DBPET in the pCR group was higher than non-pCR group (7.88 and 21.73 vs 6.22 and 16.28, $p = 0.30$ and $p = 0.15$, respectively). In contrast, post-SUVmax of the pCR group was lower than non-pCR group (0.97 and 2.06 vs 1.54 and 3.86, $p = 0.062$ and $p = 0.032$, respectively). ΔSUVmax of pCR group was higher than non-pCR group (82.23 and 88.56 vs 76.34 and 72.55, $p = 0.27$ and $p = 0.04$, respectively). Additionally, the AUC of DBPET (pre-SUVmax: 0.543, post-SUVmax: 0.725, ΔSUVmax: 0.752) was higher than WBPET (pre-SUVmax: 0.477, post-SUVmax: 0.694, ΔSUVmax: 0.549) in either time points.

Conclusions: The diagnostic accuracy of DBPET were equal to, or better than those of WBPET. DBPET might serve as a new diagnostic modality when planning therapeutic strategies for patients with breast cancer after neoadjuvant chemotherapy.

Legal entity responsible for the study: Hiroshima University

Funding: None

Disclosure: All authors have declared no conflicts of interest.

230P Efficacy and safety profile of the adriamycin/cyclophosphamide (AC) followed by docetaxel/cisplatin (DC) in locally advanced breast cancer

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Background: Neoadjuvant chemotherapy (NCT) using anthracycline - taxane based chemotherapy achieved better outcome and increase the rate of breast conservative surgery (BCS). This study evaluates the efficacy and safety profile of 4 cycles AC followed by 4 cycles of DC as NCT and detect pCR with its subsequent effect on BCS, OS, DFS and its correlation with molecular subtypes and other markers as ERCC1and Ki-67.

Methods: A prospective phase II study at the Medical Oncology Department of the National Cancer Institute (NCI), Cairo University, where 104 female patients with LABC were recruited during the period from March 2010 to July 2013 to receive eight cycles of NCT, 4 cycles of (AC) followed by 4 cycles of (DC), responding patients were referred to surgery then to radiotherapy for local control. All patients were assessable for toxicity. ER, PR, Her2neu, Ki-67 and ERCC1 were done.

Results: Median age: 51yrs, postmenopausal: 48.1%, median tumour size at presentation: 8 cm, stage IIIB: 82.7%, ER/PR positive: 78.8% and 25% were Her2neu positive. The pCR after DC according to Miller and Payne system was 20.2%, with mean tumour size:4.15$\pm$ S.D 2.703. Age and menopausal status showed statistical significant correlation with pathological response. The correlation between DFS in positive and negative ERCC1 was statistically significant; (p-value ≤ 0.01). The overall survival (OS)of the patients was 85.4% at 36 months while the disease free survival (DFS) was 85.3% at 24 months. Anaemia G2 & more was encountered in 27 patients (26%); neutropenia G2 & more was reported in 49 patients (47.1%), while Peripheral neuritis was observed in 103 patients (99%).

Conclusions: Adding Cisplatin to Docetaxel for 4 cycles after 4 cycles of Adriamycin – Cyclophosphamide improved the pCR, OS and rate of BCS. ERCC1 is a predictor marker of DFS.

Legal entity responsible for the study: IRB Committee of the national cancer institute of Cairo University

Funding: National Cancer Institute - Cairo University

Disclosure: All authors have declared no conflicts of interest.

232P Pregnancy associated breast cancer spotlights

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Background: Pregnancy associated breast cancer (PABC) is a rare entity of breast cancer. It is defined as breast cancer occurring during pregnancy or within 12 months from end of pregnancy. Though rare, it represents a very challenging situation to both the physician and patient. This retrospective study is an attempt to focus on PABC cases presenting at our institute regarding their personal, disease characteristics and type of treatment received.

Methods: This is a retrospective study conducted at Kasr-Al-Ainy oncology center "NEMROCK". The files of female patients diagnosed with breast cancer under the age of 40 in the period from January 2005 to December 2014 were retrospectively reviewed. A comparison has been conducted between PABC cases and non-pregnant cases concerning personal and disease characteristics, modality of treatment and outcomes.

Results: This study included a total of 175 patients 40 years old or younger, among them 40 were PABC cases. Twenty five percent of PABC presented with distant metastasis at first presentation while only 11.6% of the non-pregnant patients presented with metastasis (P value 0.039). Time from onset of symptoms till breast cancer diagnosis was more than 6 months in 55.6% of PABC cases in comparison to 36.3% in non-pregnant cases (P value 0.043). Concerning treatment; 32.4% of PABC cases received neoadjuvant chemotherapy while 20.7% of non-pregnant patients received it (P value 0.027). There was no statistical difference in personal and disease characteristics between pregnant and non-pregnant patients including family history, pathological subtypes, stage, grade and biological subtypes. There was no statistically significant difference in disease free survival between PABC cases and non-pregnant ones (P value 0.497).

Conclusions: PABC is associated with a late diagnosis. Although PABC patients present at later stages than non-pregnant ones and the use of neoadjuvant treatment is higher in pregnant cases, the outcome of patients with PABC is comparable to that of non-PABC of matched age.

Legal entity responsible for the study: Kasr alainy department of oncology

Funding: None

Disclosure: All authors have declared no conflicts of interest.

233TiP KEYNOTE-522: Phase III study of pembrolizumab (pembro) + chemotherapy (chemo) vs placebo + chemo as neoadjuvant followed by pembro vs placebo as adjuvant therapy for triple-negative breast cancer (TNBC)

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Background: Endogenous anticancer immunity may be enhanced with immune checkpoint inhibition by increased tumor-specific antigen release after chemo. Combining the anti–PD-1 inhibitor pembro with chemo may be an effective treatment strategy for TNBC in neoadjuvant and adjuvant settings. KEYNOTE-522 (NCT03036488) is a phase III study of neoadjuvant pembro + chemo followed by adjuvant pembro vs neoadjuvant placebo + chemo followed by adjuvant placebo in pts with TNBC.

Trial design: Eligible pts are aged ≥18 y with previously untreated, centrally confirmed, nonmetastatic TNBC, defined as combined primary tumor (T) and regional lymph node (N) staging per AJCC (investigator-assessed: T1c N1-2, T2-4 N0-2). Pts with bilateral or multifocal primary tumors or inflammatory breast cancer are allowed. ECOG PS 0-1 and adequate organ function are required. Pts with a history of invasive malignancy ≤5 y or prior therapy before study start are excluded. Approximately 855 pts will be randomly assigned to 1 of 2 arms and stratified by tumor nodal status (positive vs negative), size (T1/T2 vs T3/T4), and carboplatin choice (Q3W vs QW). In arm 1, pts will receive 4 cycles of pembro 200 mg Q3W + paclitaxel (80 mg/m^2 QW on d 1, 8, 15) + carboplatin (AUC 5 Q3W on d 1 or AUC 1.5 QW on d 1, 8, 15) and then 4 cycles of pembro + doxorubicin (60 mg/m^2 on d 1) or epirubicin (90 mg/m^2 on d 1) + cyclophosphamide (600 mg/m^2 Q3W on d 1) as neoadjuvant therapy. Definitive surgery will be 3-6 wk after the last cycle. In arm 2, placebo will replace pembro. Post-surgery, pts will receive 9 cycles of pembro or placebo as adjuvant therapy. One neoadjuvant/adjuvant cycle = 21 d; treatment is up to 17 cycles (pembro/placebo only) or until disease progression/unacceptable toxicity. Dual primary endpoints are pCR rate (ypT0/Tis ypN0) and EFS. Secondary endpoints include pCR rate (ypT0 ypN0) in all pts and in those with PD-L1+ tumors (ie, PD-L1 staining in ≥ 1% tumor cells or stroma), pCR rate (ypT0/Tis ypN0) in pts with PD-L1+ tumors, EFS in pts with PD-L1+ tumors, pCR rate (ypT0/Tis) in all pts and in those with PD-L1+ tumors, OS, and safety. Interim analyses are planned.

Clinical trial identification: EUDRACT number: 2016-004740-11 ClinicalTrials.gov, NCT03036488, January 27, 2017

Legal entity responsible for the study: Merck & Co., Inc., Kenilworth, NJ, USA

Funding: Merck & Co., Inc., Kenilworth, NJ, USA

Disclosure: P. Schmid: Honoraria: Pfizer, Boehringer, Bayer, Puma, Eisai, Celgene. Other: spouse: Genetech/Roche. J. Cortes Castan: Advisory board member: Roche, Celgene, Aztrazeneca, Cellestia Biotech, Biothera. Honoraria: Roche, Novartis, Eisai, Celgene, Pfizer. J. Bergh: Research funding; grants: Amgen, AstraZeneca, Bayer, Merck, Pfizer, Roche and Sanofi-Aventis to Karolinska Institutet/University Hospital. No personal payments. Honoraria: from UpToDate to Asklepios Medicine HB on a chapter on breast cancer diagnostics. L. Pusztai: Advisory board: Merck, Novartis, AstraZeneca. Research funding: Merck, Novartis, Roche, AstraZeneca, Seattle Genetics. Honoraria: Merck. C. Denkert: Stock ownership: Sividon Diagnostics, Cologne. Advisory board: MSD. Honoraria: Amgen, Celgene, Teva, AstraZeneca, Myriad. S. Verma: Advisory board: Amgen, Eli Lilly, AstraZeneca, Novartis, Pfizer, Roche. H.L. McArthur: Advisory board: Celgene, Merck, OBI, Spectrum Pharmaceuticals, Syndax Pharmaceuticals, Roche, Peregrine, Calithera. J. Zhao: Employment: Merck Research Lab. G. Aktan: Employment, stocks, travel: Merck & Co., Inc. T. Dang: Employment and stock: Merck Sharp & Dohme. R. Dent: Advisory board: AstraZeneca, Pfizer, Roche, Merck. Research funding: AstraZeneca. Honoaria: Eisai, Roche, Pfizer. Travel expenses: Roche, Merck, Pfizer.

234TiP KEYNOTE-355: Randomized, double-blind, phase III study of pembrolizumab (pembro) + chemotherapy (chemo) vs placebo (PBO) + chemo for previously untreated, locally recurrent, inoperable or metastatic triple-negative breast cancer (mTNBC)

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Background: In the phase Ib KEYNOTE-012 study, the anti–PD-1 antibody pembro demonstrated promising antitumor activity and acceptable safety as monotherapy in pretreated patients (pts) with PD-L1+ mTNBC. Adding pembro to chemo may enhance antitumor activity. KEYNOTE-355 (NCT02819518) is a global phase III study of pembro+chemo vs PBO+chemo in pts with previously untreated, locally recurrent, inoperable TNBC/mTNBC.

Trial design: Eligible pts are ≥18 y and have centrally confirmed, locally recurrent, inoperable TNBC or mTNBC not previously treated with chemo (prior chemo in [neo]adjuvant setting allowed); measurable disease per RECIST v1.1; ECOG PS 0-1; ≥6 mo between definitive surgery or last dose of adjuvant chemo, whichever was last; and first disease recurrence (≥12 mo if prior treatment with same-class agent). Part 1 is an open-label, unblinded safety run-in of ~30 pts distributed over 3 arms (pembro+nab-paclitaxel, pembro+paclitaxel, pembro+gemcitabine/carboplatin). Part 2 is a double-blind, PBO-controlled study of ~828 pts to be randomized 2:1 to pembro 200 mg every 3 weeks + chemo (nab-paclitaxel 100 mg/m^2 on d 1, 8, and 15 every 28 d; paclitaxel 90 mg/m^2 on d 1, 8, and 15 every 28 d; or gemcitabine 1000 mg/m^2 + carboplatin AUC 2 on d 1 and 8 every 21 d) or PBO+chemo. Crossover not allowed. Stratification factors are study chemo (taxane vs gemcitabine/carboplatin), tumor PD-L1 expression (+/-), and prior therapy with same-class agent in the (neo)adjuvant setting (yes/no). Treatment will occur for ≤35 administrations (pembro/PBO only) or until confirmed disease progression, unacceptable toxicity, withdrawal of consent, or decision to discontinue. Primary end points are safety in part 1 and PFS (by RECIST v1.1, central radiology review) and OS in part 2; secondary end points include ORR (by RECIST v1.1, central radiology review), duration of response. AEs will be graded per NCI CTCAE v4.0. Response will be assessed at wks 8, 16, 24, then at 9-wk intervals up to 1 y, and at 12-wk intervals thereafter. Interim safety analysis will occur after pts complete 1 treatment cycle in part 1.

Clinical trial identification: EUDRACT number: 2016-001432-35 ClinicalTrials.gov, NCT02819518

Legal entity responsible for the study: Merck & Co., Inc., Kenilworth, NJ, USA

Funding: Merck & Co., Inc., Kenilworth, NJ, USA

Disclosure: J. Cortes Castan: Advisory board member for Roche, Celgene, Aztrazeneca, Cellestia Biotech, Biothera. Honoraria from Roche, Novartis, Eisai, Celgene, Pfizer. Z. Guo, V. Karantza, G. Aktan: Employment and stock ownership: Merck.

235TiP A Phase Ib trial of xentuzumab and abemaciclib in patients with locally advanced or metastatic solid tumours, hormone receptor-positive (HR+), HER2-negative (HER2-) breast cancer (BC; +/-endocrine therapy), or non-small-cell lung cancer (NSCLC)

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Background: The insulin-like growth factor (IGF) and the cyclin D-cyclin-dependent kinase (CDK) 4/6-retinoblastoma pathways have been implicated in the pathogenesis and resistance mechanisms of a variety of cancers, including HR+ HER2- BC and NSCLC. IGF-ligand dependent signalling via the IGF receptor results in upregulation of cyclin D1, and thus, progression through the cell cycle, providing rationale for the simultaneous inhibition of IGF and CDK4/6. This trial assesses the maximum-tolerated dose (MTD), safety and preliminary efficacy of the IGF ligand-neutralising antibody, xentuzumab, in combination with abemaciclib, a selective inhibitor of both CDK4 and 6, +/- hormone therapy, in pts with solid tumours.

Trial design: Study BI 1280.18 (NCT03099174) is a Phase Ib multicentre, non-randomised, open-label, dose escalation trial with four dose-finding cohorts (Cohorts A–D) followed by two expansion cohorts (Cohorts E, F). Eligible pts include adults ≥18 yrs (≥20 for Japan), with measurable or evaluable disease, adequate organ

function, ECOG PS $\leq$ 1, and unresectable advanced or metastatic solid tumours after failure on standard therapy (Cohort A), postmenopausal locally advanced or metastatic HR+, HER2- BC (Cohorts B–D, F), or stage IV NSCLC after 1–2 lines of therapy and failure after platinum-based chemotherapy (Cohort E); CDK4/6 inhibitor-naïve pts (Cohorts A–E) and pts who have received prior CDK4/6 inhibitors (palbociclib or ribociclib) plus aromatase inhibitors (Cohort F) are included. Pts will receive either xentuzumab plus abemaciclib alone (Cohorts A, E) or in combination (at MTD defined for the doublet therapy) with letrozole (Cohort B), anastrozole (Cohort C), or fulvestrant (Cohorts D, F). Primary endpoints are the MTD and/or recommended phase-2-dose (RP2D; Cohorts A–D), and objective response (Cohorts E, F). Further endpoints include antitumour activity (Cohorts E, F), and pharmacokinetic outcomes (all Cohorts). This study will be conducted in the US, Europe and Japan. Pt screening is planned to start May 17; target enrolment: N≈88.

Clinical trial identification: NCT03099174; 1280.18

Legal entity responsible for the study: Boehringer Ingelheim

Funding: Boehringer Ingelheim

Disclosure: P. Lo Russo: Advisory boards: Agios: Data Safety Monitoring Board (2016-2017), Alexion: Advisory Board Member (2016-2017), Ariad: Advisory Board Member (2016-2017), GenMab: Advisory Board Member (2016-2017), Glenmark: Advisory Board Member (2016-2017), Halozyme: Data Safety Monitoring Board (2016-2017), Menarini: Advisory Board Member (2016-2017), Novartis: Advisory Board Member (2016-2017), Roche-Genentech: imCORE Alliance (2016-2019), Genentech: Advisory Board (2016-2017), CytomX: Advisory Board Member (2016-2017), Omniox: Advisory Board Member (2016-2017), Ignyta: Advisory Board Member (2016-2017). M.P. Sablin: Advisory board: Boehringer Ingelheim. E.L. Johnston: Employment: Eli Lilly and Company. Stock ownership or options: Eli Lilly and Company. T. Bogenrieder, J. Serra, K. Stucke-Straub: Employee of BI. All other authors have declared no conflicts of interest.

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BREAST CANCER, METASTATIC

236O MONARCH 3: Abemaciclib as initial therapy for patients with HR+/HER2- advanced breast cancer

237O A phase II trial of pan-HER inhibitor Poziotinib, in patients with HER2-positive metastatic breast cancer who have received at least two prior HER2-directed regimens: The results of NOV120101-203 trial

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Background: Although the introduction of HER2 directed therapy including trastuzumab, pertuzumab, lapatinib, and TDM-1 in the treatment of HER2-positive metastatic breast cancer (mBC) patients favorably changed the natural history of this disease, HER2-positive mBC will eventually progress in most patients. Poziotinib is a novel, oral pan-HER kinase inhibitor which showed potent anti-tumor activities through irreversible inhibition of HER family tyrosine kinases.

Methods: This open-label, multicenter phase 2 study was designed to evaluate the efficacy and safety of poziotinib monotherapy in patients with HER2-positive mBC who have progressed from more than 2 HER2-directed therapies. Patients received poziotinib 12 mg once daily on a 14-day on/7-day off schedule. Dose escalation up to 16 mg was allowed at appropriate time point and dose reduction to 8-10 mg were performed according to toxicities. Progression-free survival (PFS) as the primary endpoint and objective response rate (ORR), overall survival (OS), and safety were evaluated.

Results: From Apr 2015 to Feb 2016, 106 patients were enrolled in the trial from 7 institutes in Korea. The patients were median age of 50 (range: 30∼76) who had received median 4 prior anti-cancer therapies including median 2 HER2-directed therapies in the advanced or metastatic setting. Median follow up duration was 12 months. The median PFS was 4.04 months (95% CI, 2.94 - 4.40 months), and median overall survival has not been reached. The disease control rate was 75.49% (77/102) including 20 patients with confirmed partial response. The most common treatment-related AEs were (total/grade≥3) diarrhea (96.23%/14.15%), stomatitis (92.45%/12.26%), and rash (63.21%/3.77%).

Conclusions: Poziotinib showed meaningful clinical activity in heavily-treated HER2-positive mBCs. Diarrhea and stomatitis were the major toxicities leading to dose modification. Biomarker study being analyzed from pre- and on-treatment biopsies is warranted to support further on the meaningful clinical outcomes of poziotinib in HER2-positive mBC.

Clinical trial identification: NCT02418689

Legal entity responsible for the study: National OncoVenture & Hanmi Pharmaceutical Co., Ltd.

Funding: Hanmi Pharmaceutical Co., Ltd.

Disclosure: All authors have declared no conflicts of interest.

238PD A randomized, double-blind study of PF-05280014 (a potential trastuzumab biosimilar) vs trastuzumab, both in combination with paclitaxel, as first-line treatment for HER2-positive metastatic breast cancer

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Background: A biosimilar is a biologic product that is highly similar to an approved biologic drug. The humanized monoclonal antibody PF-05280014 (a potential trastuzumab biosimilar) has previously demonstrated similarity to trastuzumab in analytical, nonclinical, and clinical pharmacokinetics (PK) and safety studies. In this randomized, double-blind, efficacy and safety study, PF-05280014 was compared with trastuzumab sourced from the EU (trastuzumab-EU) as first-line treatment for patients (pts) with HER2-positive (HER2+) metastatic breast cancer (MBC).

Methods: Between 4 Apr 2014 and 22 Jan 2016, 707 pts with HER2+ MBC were randomized 1:1 to PF-05280014 or trastuzumab-EU, both given with paclitaxel (starting dose 80 mg/m^2; days 1, 8, 15 of each 28-day cycle). Trastuzumab was administered weekly until at least Week 33 (first dose 4 mg/kg; subsequent doses 2 mg/kg), with treatment continuing until progression. The primary endpoint was objective response rate (ORR; complete or partial response according to RECIST 1.1) by Week 25 and confirmed by Week 33, based on blinded central radiology review. Secondary endpoints included safety, measures of tumor control, immunogenicity, and PK.

Results: The risk ratio for ORR was 0.940 for PF-05280014 over trastuzumab-EU, with a 95% confidence interval of 0.842–1.049, which was within the pre-specified equivalence margin of 0.8–1.25. 1-yr progression-free survival (56% for PF-05280014 vs 52% for trastuzumab-EU) and 1-yr survival (88.84% vs 87.96%) were similar between groups. The safety profile, including incidence of serious adverse events, was similar in both arms, and no new safety signals were identified. After study drug initiation, all pts tested negative for antidrug antibodies, except 1 pt receiving trastuzumab-EU. Up to cycle 5 day 8, mean trough and peak serum concentrations were similar for both agents. At the cutoff for this primary analysis (24 Aug 2016), 558 pts remained ongoing in the study.

Conclusions: In pts receiving first-line treatment for HER2+ MBC, PF-05280014 was similar to trastuzumab-EU in terms of efficacy, safety, immunogenicity, and PK.

Clinical trial identification: NCT01989676; EudraCT number: 2013-001352-34

Legal entity responsible for the study: Pfizer Inc

Funding: This study was sponsored by Pfizer Inc

Disclosure: M. Pegram: Consulting: Pfizer Inc, Amgen Inc, Genentech/Roche. A. Freyman, A. Vana, F. Hilton, C. Zacharchuk, R. Ewesuedo: Employee of and holds stock or stock options in Pfizer Inc. All other authors have declared no conflicts of interest.

239PD A phase II trial of dasatinib (D) in combination with trastuzumab (T) and paclitaxel (P) in the first line treatment of HER2 positive metastatic breast cancer (MBC) patients (pts): GEICAM/2010-04

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Background: In HER2 overexpressing MBC around 40% of pts treated with T-based regimens do not respond and half of them progress within a year. The combination of the SRC inhibitor D and T is synergistic in preclinical models. We conducted a phase II trial combining D with a standard first line treatment with T/P.

Methods: Pts with HER2+ MBC (by central laboratory) were included. First line treatment consisted of 28-day cycles with T 2mg/kg weekly, P 80mg/m2 (3 weeks on/1 week off) and D 100mg once daily administered in first line until radiologic or symptomatic progression (PD) or unacceptable toxicity. Primary objective was objective response rate (ORR); secondary objectives were safety, other efficacy variables (Clinical Benefit Rate (CBR), Time to Progression (TTP), Progression Free Survival (PFS)) and pharmacodynamic biomarkers (phosphorylated (p)-AKT, and p-SRC) in peripheral mononuclear cells (PBMCs).

Results: Twenty-nine pts were included; median age was 49 years (31-81), 12 pts (41%) were premenopausal, 22 (76%) had hormone-receptor positive tumors and 23 (79.3%) had visceral disease. The median number of cycles was 12 (1-35), 9 pts discontinued treatment due to PD, 6 for adverse events, 6 due to investigator/sponsor criteria and 8 due to other reason. The ORR was 79.3% (95% CI 60.3-92) and the CBR was 82.8% (95% CI 64.2-94.2). Median TTP was 23.9 months (95% CI 14.9-not reached (NR)) and median PFS was 23.9 months (95% CI 10.3-NR). The mean relative dose intensity of D, T and P was 98.3%, 99.8% and 89.7% respectively. G2-3 decrease in ejection fraction was seen in 10.3% (n = 3) and 24.1% (n = 7) of pts. No G4 toxicity was seen. G3 toxicities were limited to: fatigue, hypertension, neutropenia and hyponatremia (6.9% [n = 2] each). Phosphorylated SRC and AKT were reduced in PBMCs after 8h (4.4 and 1.9 folds, respectively) of D administration in cycle 1 day 1 in 16 assessed pts.

Conclusions: D can be safely combined with T and P and the combination is effective with a ORR that reached almost 80% of patients. We observed decreased levels of p-SRC and p-AKT in PBMCs in patients treated with D, as previously described in preclinical models.

Clinical trial identification: NCT01306942

Legal entity responsible for the study: GEICAM Spanish Breast Cancer Group

Funding: Bristol-Myers Squibb (BMS)

Disclosure: All authors have declared no conflicts of interest.

240PD Comprehensive genomic profiling of primary and metastatic CDH1 mutated classic and pleomorphic invasive lobular breast carcinomas reveals markers of hormonal therapy resistance and opportunities for targeted therapies

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Background: Although invasive lobular breast cancer (ILC) is typically combined with the far more frequent ductal disease for clinical trials and research studies. We queried whether classic (CILC) and its uncommon pleomorphic variant (PILC) featured unique genomic alterations (GA) which could influence therapy for patients with relapsed and refractory disease.

Methods: From a series of 10,784 invasive breast carcinomas DNA was extracted from 40 µm of FFPE sections of 454 (4%) *CDH1* mutated ILC including 428 classic (CILC) (94%) and 26 pleomorphic (PILC) (6%) subtypes. CGP was performed on hybridization-captured, adaptor ligation-based libraries (mean coverage depth >600X) for up to 315 cancer-related genes. Total mutational burden (TMB) was determined on 1.2 Mbp of sequenced DNA.

Results: Median age at 63 years was similar for both CILC and PILC (see Table). Clincal ER+ status (p) was higher in CILC and HER2+ status was higher in PILC ($P < 0.0001$). *ESR1* substitution GA were significantly higher in CILC and the frequency of *ESR1* GA was significantly higher in CILC exposed to hormonal therapy (metastasis biopsies) than in pre-treatment primary tumors ($P < 0.0001$). *ERBB2* GA (amp + non-amp) detected by CGP were higher in PILC than CILC in both pre-and post-treatment samples ($P < 0.0001$ for both). *ERBB2* GA nearly doubled after hormonal treatment in both CILC and PILC. *PIK3CA* GA were similarly the most frequent GA in both CILC and PILC, but *TP53* GA were significantly more frequent in PILC than CILC. Median TMB was higher in PILC than CILC and TMB $\geq$ 15 mut/MB was more than twice as frequent in PILC than CILC ($P = 0.046$). Patients with post primary therapy associated *ESR1* and *ERBB2* GA responding to precision therapies will be presented.

Table: 240PD

	CILC (428)	PILC (26)
Median Age	63	63
*ER +	98%	74%
*HER2 IHC/FISH+	12 (3%)	6 (22%)
ESR1 GA Primary Pre-Rx	6%	0%
ESR1 GA Metastatic Post-Rx	17%	0%
ERBB2 GA Primary Pre-Rx	7%	18%
ERBB2 GA Metastatic Post-Rx	12%	34%
Other Significant GA	*PIK3CA* (55%), *CCND1* (21%), *TP53* (17%), *ARID1A*, *AKT3*, *MDM4*, *PTEN* (all 11%)	*PIK3CA* (58%), *TP53* (30%), *AKT1* 22%), *FGFR4*, *CCND1*, *PTEN* (all 17%)
TMB median (mut/Mb)	2.7	3.6
TMB $\geq$ 15%	8%	19%

*when clinical status available.

Conclusions: Both CILC and PILC show differences in GA in pre-treatment primary vs metastatic lesions in important genes such as ESR1 and ERBB2 likely reflecting the impact of primary therapies. Relapsed CILC is more often driven by ESR1 GA and PILC by ERBB2 GA. Both the CILC and PILC groups have subsets with high TMB, more frequent in PILC, indicating potential for immunotherapies for these patients.

Legal entity responsible for the study: Jeffrey S Ross

Funding: None

Disclosure: J.S. Ross, V.A. Miller, P. Stephens: Employee, leader and owns stock in Foundation Medicine. L.M. Gay, J.A. Elvin, J-A. Vergilio, S. Ramkissoon, E. Severson, S. Daniel, G.M. Frampton, D. Fabrizio, A.B. Schrock, S.M. Ali, J. Chung, J. Suh: Employee and owns stock in Foundation Medicine.

241PD BEECH: A randomised Phase 2 study assessing the efficacy of AKT inhibitor AZD5363 combined with paclitaxel in patients with ER+ve advanced or metastatic breast cancer, and in a PIK3CA mutant sub-population

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Background: AZD5363 (AZD) potently and selectively inhibits AKT1–3. *PIK3CA* mutations increase sensitivity to AZD in vitro and in vivo. We conducted a randomised Phase 2 trial (NCT01625286), to compare the efficacy of AZD versus placebo, in combination with weekly paclitaxel, in advanced or metastatic ER+ve/HER2−ve breast cancer, and in a PIK3CA mutation sub-population (*PIK3CA*+).

Methods: Female patients (N = 110) aged ≥18 years with ER+ve/HER2−ve advanced or metastatic breast cancer who had received no prior chemotherapy in the advanced or metastatic setting were enrolled. Patients were randomised 1:1, stratified by PIK3CA mutation status (*PIK3CA*+ vs *PIK3CA*− in tissue or circulating tumour DNA), to receive paclitaxel 90 mg/m^2 i.v. once weekly for 3 weeks out of 4, plus oral AZD 400 mg, or matched placebo twice daily 4 days on, 3 days off, starting on the day after each paclitaxel administration. Enrolment was capped to ensure 50 *PIK3CA*+ patients were enrolled. Progression status and tumor response (RECIST 1.1) was assessed every 12 weeks. The primary endpoint was investigator-assessed progression-free survival (PFS).

Results: Median PFS was 10.9 months (95% CI 8.3–12.4) on AZD plus paclitaxel versus 8.4 months (95% CI 8.2–10.8) on placebo plus paclitaxel (HR 0.80, 80% CI 0.6–1.06, p = 0.31). In the *PIK3CA*+ subgroup, median PFS was 10.9 months (95% CI 8.7–11.5) on AZD plus paclitaxel versus 10.8 months (95% CI 8.3–14.3) on placebo plus paclitaxel (HR 1.11, 80% CI 0.73–1.68, p = 0.76). Objective response rate was 59% on AZD plus paclitaxel versus 57% on placebo plus paclitaxel. The most common adverse events were diarrhoea (76% AZD vs 27% placebo), alopecia (52% vs 49%), nausea (39% vs 24%) and anaemia (33% vs 27%). Adverse events grade 3 or higher included diarrhoea (24% vs 2%), hyperglycaemia (13% vs 0%) and neutropenia (11% vs 9%). Discontinuation rates due to adverse events were 13% on AZD and 7% on placebo.

Conclusions: Adding AZD to weekly paclitaxel did not prolong PFS in the overall population or *PIK3CA*+ subgroup of ER+ve/HER2−ve advanced or metastatic breast cancer.

Clinical trial identification: ClinicalTrials.gov NCT01625286 Other Study ID Numbers: D3610C00002; 2011-006312-31 (EudraCT Number)

Legal entity responsible for the study: AstraZeneca (Study Director: Justin PO Lindemann)

Funding: AstraZeneca

Disclosure: N. Turner: Advisory board honoraria and research funding from AstraZeneca. A. Armstrong: Fees from Roche and Syndax for consulting/advisory roles. M-P. Sablin: Within the last year, travel/accommodation expenses paid/reimbursed by Pfizer. K. Tamura: As the responsible project lead (e.g., Principal Investigator), Direct research support from AstraZeneca, Daiichi Sankyo, MSD and Pfizer. A. Gomez Villanueva: Research funding from AstraZeneca, PPD, Quintiles. J.A. Pérez-Fidalgo: Fees from AstraZeneca, Ipsen, Novartis, Pfizer and Roche for participation in speaker bureaus. Travel/accommodation expenses paid/reimbursed by AstraZeneca, Roche and Sandoz. A. Foxley, J. Lindemann, R. Maudsley, P. Rugman: Employee at AstraZeneca (and shareholder). E. Outhwaite: Employee of AstraZeneca via freelance contract with Aptus Clinical. M. Pass: Employee at AstraZeneca (and shareholder with intellectual property interests). G. Schiavon: Employee at AstraZeneca. M. Oliveira: Fees from Genentech/Roche and PUMA Biotechnology for consulting/advisory roles. Research funding to the institution from AstraZeneca and Genentech/Roche. All other authors have declared no conflicts of interest.

242PD Initial results of a phase 1 dose expansion cohort of M6620 (formerly VX-970), an ATR inhibitor, in combination with cisplatin in patients with advanced triple-negative breast cancer NCT02157792)

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Background: ATR is a regulator of the cellular response to replication stress and signals DNA damage repair through homologous recombination. Many cancers depend on ATR to survive DNA damage. VX-970 is a potent, selective inhibitor of ATR with preclinical anticancer activity in combination with DNA-damaging chemotherapy in TNBC models. Given the prevalence of DNA damage repair defects in TNBC, this study evaluated the safety and efficacy of VX-970 in combination with Cis in an expansion cohort of pts with BRCA1/2 wild-type mTNBC.

Methods: Eligible pts had advanced ER-, PR-, and HER2- BC with 0-2 prior non–platinum-based therapies. First line pts were eligible if relapse occurred ≥ 3 months after prior (neo)adjuvant chemotherapy. Measurable disease per RECIST 1.1 was required. Of a maximum 50 pts planned for enrollment, ≥30 were required to be BRCA1/2 germline wild-type and to have basaloid molecular subtype tumors on central testing. Pts received intravenous Cis 75 mg/m^2 on day 1 with VX-970 140 mg/m^2 on days 2 and 9 of each 21-day cycle. In pts intolerant to Cis or at investigator's discretion, treatment could be switched to carboplatin AUC 5 with VX-970 90 mg/m^2.

Results: At the time of this analysis, 35 female pts with mTNBC who received ≥1 cycle of study drug were included in the safety set (median age, 48 y [range 35-74 y]). Grade ≥3 related TEAEs occurred in 16/35 pts: neutropenia (n = 8), anemia (n = 5), vomiting (n = 4), nausea (n = 3), and 1 pt each with thrombocytopenia, neutrophil count decreased, platelet count decreased, hypokalemia, generalized weakness, rigors, and acute kidney injury. Of these 35 pts, 18 were BRCA1/2 wild-type and had basaloid TNBC with at least 1 baseline scan and 1 on-treatment scan at the time of the data cut. Preliminary objective response rate was 38.9% (n = 7 [all partial response]), and disease control rate (CR+PR+SD) was 72.2% (n = 13).

Conclusions: Combination VX-970 and Cis shows encouraging antitumor activity and tolerability in mTNBC. The study is ongoing; updated safety and efficacy results will be presented.

Clinical trial identification: NCT02157792

Legal entity responsible for the study: Vertex Pharmaceuticals Incorporated

Funding: Vertex Pharmaceuticals Incorporated

Disclosure: M.L. Telli: Advisory role for AstraZeneca, PharmaMar, Tesaro, and Vertex, and contracted research with Calithera, Genentech, Medivation, Novartis, OncoSec, Pfizer, PharmaMar, Tesaro, and Vertex. E. Dean: Employee of AstraZeneca. Research funding from Vertex. S.M. Tolaney: Research funding from Genentech, Merck, Pfizer, Novartis, Lilly, Exelixis, Nektar, and AstraZeneca. R. Tang, M.S. Penney, G. Conboy, S.Z. Fields: Employee of Vertex Pharmaceuticals Incorporated and may own stock or stock options in that company. J. Pollard: Employee of Vertex Pharmaceuticals Limited and may own stock or stock options in that company. G. Shapiro: Research funding from Vertex and Pfizer. Advisory role for Vertex, G1 Therapeutics, Lilly, Millenium/Takeda, Tesaro, Chugai, and EMD Serono. All other authors have declared no conflicts of interest.

243PD OlympiAD: Further efficacy outcomes in patients with HER2-negative metastatic breast cancer and a germline BRCA mutation receiving olaparib monotherapy vs standard single-agent chemotherapy treatment of physician's choice

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Background: The Phase III OlympiAD study (NCT02000622) in patients with metastatic breast cancer (mBC) and a germline *BRCA* mutation (g*BRCA*m) showed a statistically significant progression-free survival (PFS) benefit for olaparib monotherapy over chemotherapy treatment of physician's choice (TPC; hazard ratio [HR] 0.58; 95% CI 0.43, 0.80; $P<0.001$; 7.0 vs 4.2 months for olaparib vs TPC, respectively). We report further efficacy outcomes for objective response, target lesion shrinkage and tumour burden.

Methods: OlympiAD was a randomized, open-label, Phase III study of olaparib monotherapy vs TPC in HER2-negative mBC patients with a g*BRCA*m who had received ≤2 chemotherapy lines in the metastatic setting. Patients were randomized 2:1 to olaparib tablets (300 mg bid) or single-agent TPC (capecitabine, eribulin or vinorelbine). Patients had ≥1 lesion suitable for assessments according to modified RECIST 1.1. The primary endpoint was PFS by blinded independent central review.

Results: 302 patients were randomized to olaparib (n = 205) or TPC (n = 97). In patients with measurable disease, objective response rate (ORR) was 59.9% for olaparib patients (n = 167; complete response [CR] 9.0%, partial response [PR] 50.9%, stable disease ≥5 weeks [SD] 25.1%; progressive disease [PD] 15.0%) and 28.8% for TPC patients (n = 66; CR 1.5%, PR 27.3%, SD 37.9%, PD 33.3%). Median best percentage change from baseline in target lesion size was −45.1% for olaparib and −14.8% for TPC.

Table 243PD Subgroup analyses for PFS by baseline tumour burden and location are shown in the Table.

	Olaparib 300 mg bid	Chemotherapy TPC
Tumour burden		
1 metastatic site, n	46	25
Median PFS, months	8.4	4.2
HR (95% CI)	0.62 (0.35, 1.13)	
≥2 metastatic sites, n	159	72
Median PFS, months	6.5	3.0
HR (95% CI)	0.59 (0.43, 0.82)	
Tumour location		
Bone-only metastases, n	16	6
Median PFS, months	11.2	–
HR (95% CI)	Not calculated	
Other metastatic sites,* n	189	91
Median PFS, months	6.6	3.9
HR (95% CI)	0.60 (0.46, 0.81)	

*Includes both bone and other tumour locations

Conclusions: Olaparib monotherapy in OlympiAD led to a doubling of ORR vs TPC and a larger reduction in target lesion size, indicating a more pronounced depth of response in HER2-negative g*BRCA*m mBC patients. PFS was longer with olaparib than with TPC, irrespective of tumour burden and location.

Clinical trial identification: NCT02000622, 15 June 2017

Legal entity responsible for the study: AstraZeneca

Funding: AstraZeneca

Disclosure: S. Delaloge: Honoraria, research funding, consulting, and travel, expenses and accommodation from Novartis, Roche, AstraZeneca, Pfizer, GE Healthcare, and Puma Biotechnology. P.F. Conte: Speakers' bureau with Roche-Genentech, Novartis, AstraZeneca and Lilly, travel, accommodations, and expenses from Novartis, Celgene and AstraZeneca, and research funding from Roche, Novartis and Merck Serono. S-A. Im: Consultancy for Novartis, Hanmi and Spectrum Pharmaceuticals. E. Senkus-Konefka: Honoraria from Amgen, AstraZeneca, Pfizer, Pierre Fabre and Roche, and consulting for Amgen, AstraZeneca, Pfizer, Pierre Fabre and Roche. S.M. Domchek: Research funding to the University of Pennsylvania from AstraZeneca, Clovis Oncology, AbbVie and Pharmamar. N. Masuda: Honoraria from Chugai Pharma, AstraZeneca and Kyowa Hakko Kirin, and research funding from Chugai Pharma, AstraZeneca, Kyowa Hakka Kirin, MSD, Novartis, Pfizer and Lilly. N. Tung: Patents, royalties and other intellectual property with Ambry Genetics, and research funding from Myriad Genetics. A. Armstrong: Consulting for Roche and Syndax. W. Wu, C. Goessl, S. Runswick: Employee of and stock ownership in AstraZeneca. M. Robson: Consultancy for AstraZeneca and McKesson, travel, accommodation and expenses from AstraZeneca, honoraria from AstraZeneca and research funding from AstraZeneca, AbbVie, Myriad Genetics and Medivation. All other authors have declared no conflicts of interest.

244PD Everolimus (EVE) + letrozole (LET) in patients (pts) with estrogen receptor-positive (ER+), human epidermal growth factor receptor 2-negative (HER2−) advanced breast cancer (ABC): Progression-free survival (PFS) subgroup analyses in BOLERO-4

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Background: The BOLERO-4 study demonstrated clinical benefit and an acceptable safety profile with first-line (1L) EVE + LET in postmenopausal pts with ER+, HER2− ABC. Pre-specified subgroup analyses evaluated PFS in pt subgroups: age (<65 years vs ≥ 65 years), visceral metastases (yes vs no), and bone-only lesions at baseline (yes vs no).

Methods: BOLERO-4 is an open-label, Phase II, multicenter, international, single-arm trial. Postmenopausal pts with ER+, HER2− ABC, with no prior therapy for advanced disease, received EVE 10 mg/day + LET 2.5 mg/day until disease progression, unacceptable toxicity, or withdrawal of consent. The primary endpoint was locally assessed 1L PFS on the overall full analysis set (FAS). Here we report 1L PFS data that was assessed based on the aforementioned pt subgroups. BOLERO-4 is registered with ClinicalTrials.gov (NCT01698918).

Results: At the data cut-off (Dec 17, 2016), 202 pts with ABC were enrolled for 1L treatment with EVE + LET. Median PFS, and 18- and 24-month Kaplan−Meier-estimated PFS rates were similar to the FAS irrespective of pt age, presence/absence of visceral metastases, or presence/absence of bone-only lesions at baseline (Table). The distribution and frequency of all-grade adverse events (regardless of causality) among pts aged <65 and ≥65 years was comparable with the overall population.

Conclusions: Treatment benefit with EVE + LET in the 1L setting was maintained across pt subgroups and was consistent with that observed in the FAS of the BOLERO-4 study. EVE + LET, therefore, is an effective 1L treatment for ER+, HER2− ABC, irrespective of pt age, visceral metastases, or bone-only lesions. These data support the potentially important role of EVE in the ABC treatment landscape.

Clinical trial identification: Protocol version 04

Legal entity responsible for the study: Novartis Pharmaceuticals Corporation

Funding: Novartis Pharmaceuticals Corporation

Disclosure: T. Bachelot: Research funding from Roche, Novartis. Consultant for and travel expenses from AstraZeneca, Roche, Novartis, Pfizer. M. Royce: Research funding and honoraria from Novartis. C. Villanueva: Advisory board member for Novartis Pharmaceuticals Corporation. F. Melo Cruz: Research funding from Novartis, Janssen, Roche, Celgene. Travel, accommodation, expenses from Janssen. C. Falkson: Research funding from Novartis, Oncothyreon, Genentech, EMD Serono. Consultant for and honoraria from Biotheranostics. J. Jeong: Research funding from Dong-A, Boryung,

Table: 244PD

	FAS	Age		Visceral metastases		Bone-only lesions at baseline	
	N = 202	<65 years (n = 108)	≥65 years (n = 94)	Yes (n = 123)	No (n = 79)	Yes (n = 28)	No (n = 174)
No. of PFS events, n (%)	108 (53.5)	68 (63.0)	40 (42.6)	65 (52.8)	43 (54.4)	12 (42.9)	96 (55.2)
Median PFS (95% CI), months	22.0 (18.1–25.1)	20.3 (16.5–23.9)	24.0 (18.4–29.7)	22.1 (16.6–25.8)	20.3 (16.6–25.9)	23.7 (9.4–NE)	21.7 (18.1–25.7)
Kaplan–Meier-estimated PFS rate, % (95% CI) 18-month	58.8 (50.9–65.8)	54.6 (44.2–63.8)	64.6 (52.1–74.6)	57.8 (47.5–66.8)	60.3 (47.5–70.8)	54.4 (31.4–72.6)	59.4 (50.9–66.9)
Kaplan–Meier-estimated PFS rate, % (95% CI) 24-month	42.9 (35.0–50.5)	40.0 (30.0–49.7)	46.7 (33.8–58.6)	43.7 (33.5–53.5)	41.8 (29.5–53.6)	48.3 (25.7–67.7)	42.3 (33.9–50.4)

CI, confidence interval; NE, not estimable.

LG Life Sciences, Antigen. Honoraria from Roche, Alvogen, Novartis, Pfizer, Covidien. C.H. Arce: BD and Novartis employee. Stocks with BD. A. Ridolfi: Novartis Pharma S.A.S. employee. C. Lin: Novartis employee and stocks. F. Cardoso: Research funding for clinical trials by institution. Consultant for Astellas/Medivation, AstraZeneca, Celgene, Daiichi-Sankyo, Eisai, GE Oncology, Genentech, GSK, MacroGenics, Merck, Merus BV, Novartis, Pfizer, Pierre-Fabre, Roche, Sanofi, Teva. All other authors have declared no conflicts of interest.

245PD Duration of response and tumor shrinkage with first-line ribociclib + letrozole in postmenopausal women with HR+, HER2– ABC

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Background: The Phase 3 MONALEESA-2 study (NCT01958021) demonstrated that addition of ribociclib (RIB; cyclin-dependent kinase 4/6 inhibitor) to letrozole (LET) significantly improved progression-free survival (PFS) in patients (pts) with hormone receptor-positive (HR+), HER2-negative (HER2–) advanced breast cancer (ABC). RIB benefit was observed as early as 8 weeks. Here we evaluate duration of response (DoR) and tumor shrinkage.

Methods: Postmenopausal women (N = 668) with HR+, HER2– ABC and no prior systemic therapy for ABC were randomized to RIB (600 mg/day; 3 weeks on/1 week off) + LET (2.5 mg/day; continuous) or placebo (PBO) + LET. Pts had measurable disease or ≥ 1 predominantly lytic bone lesion. Primary endpoint was PFS; DoR was an exploratory endpoint. Tumor assessments were conducted every 8 weeks for the first 18 months. For tumor shrinkage analyses, pts were grouped by quartiles (Q) for best % change in target lesion; pts were excluded from this analysis if best % change was unavailable or contradicted by overall response of unknown/progressive disease.

Results: Of 501 pts with measurable disease, 135 (53%) vs 91 (37%) pts had a complete response or partial response in the RIB + LET vs PBO + LET arm, respectively. At a median follow-up of 15.3 months, median DoR was not reached in either arm. Tumor shrinkage was evaluable in 443 (66%) pts. Pt characteristics were well-balanced in both arms and irrespective of tumor shrinkage, apart from *de novo* ABC in Q2–Q3 (RIB + LET vs PBO + LET; 46% vs 30%) and visceral disease in ≤Q1 (64% vs 84%). A higher proportion of pts in the RIB + LET vs PBO + LET arm experienced a best % change of at least 53% (**Table**). In all evaluable pts, mean % change in tumor size was greater in the RIB + LET vs PBO + LET arm at each tumor evaluation over the first 18 months.

Table: 245PD

Q	Cut-off	Corresponding best % change in tumor size	RIB + LET n=231	PBO + LET n = 212
≤Q1	≤25%	At least –53%	73 (32%)	38 (18%)
Q1–Q2	>25% to ≤ 50%	Between –53% and –33%	64 (28%)	52 (25%)
Q2–Q3	>50% to ≤ 75%	Between –33% and –12%	52 (23%)	54 (25%)
>Q3	>75%	Less than –12%	42 (18%)	68 (32%)

Conclusions: In postmenopausal women with HR+, HER2– ABC, first-line RIB + LET prolonged PFS and was associated with a greater degree of tumor shrinkage vs PBO + LET.

Clinical trial identification: NCT01958021

Legal entity responsible for the study: Novartis Pharmaceuticals Corporation

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246PD Efficacy of two times four versus continuous eight cycles of paclitaxel/bevacizumab as first-line chemotherapy in metastatic breast cancer: The Stop&Go study of the Dutch Breast Cancer Research Group (BOOG)

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Background: The primary goal of this non-inferiority trial was to determine if an intermittent treatment regimen was not inferior to a continuous regimen, in first-line treatment of patients with HER2-negative, incurable, metastatic or unresectable locally advanced breast cancer.

Methods: Patients were randomised to receive 8 cycles or 2x4 cycles of paclitaxel/bevacizumab on days 1, 8 and 15 every 4 weeks, both with continuation of bevacizumab

once every 21 days until disease progression or unacceptable toxicity. If progressive disease occurred ≥ 3 months after the initial 4 cycles with paclitaxel/bevacizumab in the intermittent arm, another 4 cycles were given. If progressive disease occurred in the continuous arm or < 3 months after the initial 4 cycles in the intermittent arm, second-line treatment was started. The primary endpoint was progression-free survival (PFS), secondary endpoints included overall survival (OS). Intention-to-treat and per-protocol analyses were performed using a proportional hazards regression model. The two-sided 95% confidence interval (CI) for the hazard ratio (HR) was calculated and the upper limit was compared with the non-inferiority margin of 1.34.

Results: The intention-to-treat population comprised of 420 patients. The total median PFS in first-line treatment was 10.7 months (95% CI 7.03 - 12.42) for the intermittent regimen and 9.7 months (95% CI 8.94 - 10.28) for the continuous regimen (HR for disease progression or death [intermittent vs. continuous], 1.006; 95% CI 0.743 - 1.361). Results on OS were similar with a HR of 1.312 (95% CI 0.959 - 1.794). The per-protocol analysis showed comparable results. Safety results and actually delivered treatments did not reveal unexpected findings and will be presented at the meeting.

Conclusions: Intermittent first-line treatment with paclitaxel/bevacizumab is not non-inferior to continuous scheduling regarding PFS in patients with HER2-negative incurable locally advanced or metastatic breast cancer. Analysis of the secondary endpoint OS supported this conclusion. Therefore, intermittent first-line treatment cannot be recommended over continuous scheduling.

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Legal entity responsible for the study: Dutch Breast Cancer Research Group (BOOG)

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247P A single-arm, phase ii study assessing the efficacy of pembrolizumab (pembro) plus radiotherapy (RT) in metastatic triple negative breast cancer (mTNBC)

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Background: Overall response rates of 13-19% have been reported with checkpoint inhibitor monotherapy in chemotherapy-resistant, PD-L1-positive mTNBC. RT is frequently used to enhance local control in mTNBC and has been reported to induce distant (abscopal) tumor responses when combined with immunotherapy. In this study we evaluate the safety and efficacy of RT combined with the anti-PD-1 inhibitor, pembro, in a single-arm, two-stage, phase II study in mTNBC (NCT02730130).

Methods: Eligible women had biopsy-proven mTNBC, ECOG performance status 0-2, and ≥2 measurable sites of metastatic disease with at least 1 site requiring RT. A total RT dose of 3000 cGy was delivered in 5 daily fractions. IV pembro was given at 200mg within 3 days of first RT fraction then every 3 weeks until disease progression. The primary endpoint was overall response rate at week 13 in the non-irradiated lesions by RECIST v1.1. Secondary endpoints included safety and overall survival. Tumor biopsies were obtained at baseline and at week 7. PD-L1 expression was not required for study entry.

Results: As of May 1, 2017, the study has completed enrollment (N = 17) with 4 women on treatment pending 13-week evaluation. Median age was 52y (range 37-73y). Median number of prior therapies received for metastatic disease was 3 (range 0 to 8). Of the 7 women not evaluable at 13 weeks: 5 died secondary to disease-related complications (at weeks 2, 6, 7, 8, and 9) and 2 came off study due to disease progression prior to week 13. Of the 6 women evaluable at week 13, 2 (33%) had a partial response (PR), 1 (17%) had stable disease (SD) and 3 (50%) had disease progression. The 2 PRs represented 76% and 75% decreases in tumor burden by RECIST v1.1 durable for 21 and 31 weeks, respectively. SD response was durable for 30 weeks. Common toxicities were mild and included fatigue, myalgia and nausea.

Conclusions: The combination of pembro and RT was well-tolerated. This is a poor prognosis population with 5/13 (38%) evaluable patients dying within 12 weeks of study entry. However, durable responses were observed outside of the RT field in 2/6 (33%) patients who were unselected for PD-L1 expression and evaluable at 13 weeks. Safety and toxicity data for all study patients will be presented.

Clinical trial identification: NCT02730130

Legal entity responsible for the study: Memorial Sloan Kettering Cancer Center

Funding: Merck

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248P Impact of prior treatment on palbociclib plus letrozole (P+L) efficacy and safety in patients (pts) with estrogen receptor-positive/human epidermal growth factor receptor 2-negative (ER+/HER2–) first-line advanced breast cancer (ABC): A PALOMA-2 subgroup analysis

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Background: PALOMA-2 confirmed the efficacy and safety of P+L vs placebo (PBO)+L in pts with treatment-naive ER+/HER2– ABC (Finn *NEJM*, 2016). Here, we report efficacy and safety among P+L-treated pts in 2 subgroups of either exposed or not exposed to prior neo(adjuvant) endocrine therapy (ET) and/or chemotherapy (CT).

Table: 248P

	Prior ET n = 249	No Prior ET n = 195	Prior CT n = 213	No Prior CT n = 231
Pt characteristics				
Median age, y	60	64	58	65
White/Asian race, %	75/17	81/11	77/16	78/14
Non-Hispanic or Latino, %	87	87	86	87
Median duration since diagnosis, y	8.8	0.2	8.8	0.2
Exposure to P				
Median number of cycles (range)	18 (1-37)	21 (1-37)	19 (1-37)	21 (1-37)
Median treatment duration, mo (range)	18.66 (0.03-33.84)	20.76 (0.07-34.07)	18.89 (0.03-34.07)	20.37 (0.07-33.18)
Median average daily P dose, mg (range)	125 (77-125)	125 (78-125)	125 (77-125)	125 (78-125)
Ef˚cacy endpoints for P+L vs PBO+L				
Median PFS, mo Hazard ratio (95% CI)	22.2 vs 11.3 0.53 (0.40-0.70)	25.7 vs 19.6 0.63 (0.44-0.90)	22.4 vs 13.7 0.53 (0.40-0.72)	25.7 vs 17.0 0.61 (0.44-0.84)
Objective response rate, % Odds ratio (95% CI)	33.7 vs 27.0 1.38 (0.84-2.29)	52.8 vs 44.8 1.38 (0.82-2.33)	36.2 vs 30.3 1.30 (0.78-2.22)	47.6 vs 38.9 1.43 (0.88-2.32)
Rate of clinical benefit, % Odds ratio (95% CI)	81.5 vs 66.7 2.21 (1.31-3.70)	89.2 vs 75.0 2.76 (1.37-5.56)	81.7 vs 70.6 1.85 (1.04-3.29)	87.9 vs 69.9 3.12 (1.71-5.71)

NE=not estimable.

Methods: Postmenopausal women (N = 666) were randomized 2:1 to receive P (125 mg QD; 3 wk on, 1 wk off) + L (2.5 mg QD; continuously) or PBO+L. Prior neo(adjuvant) ET/CT with curative intent was allowed; prior ET or CT for recurrent advanced or metastatic disease was not. The primary endpoint was investigator-assessed progression-free survival (PFS); other key endpoints included response rates and safety. Exposure to P among subgroups is also presented.

Results: At baseline, 249/444 pts (56%) in the P+L arm had received prior ET and 213 (48%) had received prior CT (Table). Pts previously treated were slightly younger vs those not previously treated. Exposure to P+L was similar across subgroups. In P+L-treated pts, median PFS was 22.2/25.7 mo with prior ET/no prior ET and 22.4/25.7 mo for prior CT/no prior CT. The significant clinical benefit of P+L vs PBO+L remained regardless of prior ET/CT exposure. Across all subgroups, the incidence of all-causality adverse events (AEs) was similar; neutropenia was the most frequent AE. AEs leading to permanent discontinuation occurred in < 10% of pts.

Conclusions: Regardless of prior (neo)adjuvant treatment, P+L significantly prolonged PFS vs PBO+L and demonstrated consistent efficacy in pre-treated and non–pre-treated subgroups of postmenopausal pts with ER+/HER2– ABC. Tolerability was similar across subgroups and consistent with the known safety profile of P.

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Legal entity responsible for the study: Pfizer

Funding: Pfizer

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249P Analysis of overall survival by tumor response in MONARCH 1, a phase 2 study of abemaciclib, a CDK4 and CDK6 inhibitor, in women with HR+/HER2- metastatic breast cancer (MBC) after chemotherapy for advanced disease

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Background: Abemaciclib is a selective inhibitor of CDK4 and CDK6 dosed orally on a continuous schedule. Abemaciclib monotherapy (MONARCH 1) has demonstrated antitumor activity in heavily pretreated patients with HR+/HER2- MBC in terms of objective response rate (ORR= CR + PR) (19.7%; 95% CI: 13.3, 27.5), disease control rate (DCR= CR + PR + SD) (67.4%), and clinical benefit rate (CBR= CR + PR + SD ≥ 6 months [m]) (42.4%). At 18 m minimum follow-up, the median progression-free survival (PFS) was 5.95 m (95% CI: 4.21, 7.50) and median overall survival (OS) was 22.3 m (95% CI: 17.7, NR). Treatment was well tolerated. The results from exploring associations between ORR and OS are reported.

Methods: The primary objective of MONARCH 1 (NCT02102490) was to evaluate ORR per RECIST 1.1. Secondary objectives included duration of response (DoR), PFS, OS, DCR, CBR and safety. To explore whether responders have a better survival than nonresponders, a Cox proportional hazards model with responder status as a time-dependent covariate was used. A multivariable analysis using Cox regression model including baseline factors (ECOG PS, age, PgR status, liver mets, pleural/peritoneal mets, number of chemotherapies, prior capecitabine, number of metastatic sites), and response status was conducted to adjust for any differences in baseline prognostic factors in the two groups. As a supportive analysis, a landmark analysis at 6 m was performed.

Results: 26/132 patients (19.7%) achieved a best response of PR (responders). In the analysis where response was included as a time dependent covariate, patients who responded had a better OS (HR 0.31; 95% CI: 0.12, 0.77; p=.01) compared with nonresponders. After adjusting for potential baseline prognostic factors, results were consistent (HR 0.31; 95% CI: 0.12, 0.79; p=.01). Landmark analysis at 6 m supported results from previous analyses (HR 0.34; 95% CI: 0.12, 0.95; p=.04).

Conclusions: An association between ORR and OS was observed. Responders have a better OS compared to nonresponders.

Clinical trial identification: NCT02102490

Legal entity responsible for the study: Eli Lilly and Company

Funding: Eli Lilly and Company

Disclosure: J. Cortés: Honoraria: Roche, Novartis, Eisai, Celgene, Pfizer. Consulting/advisor: Roche, Celgene, AztraZeneca, Cellestia Biotech, Biothera. H.S. Rugo: Grants/Research Support: GSK, Genentech/Roche, Novartis, Pfizer, Merck, Eisai, Plexxikon, Macrogenics, Lilly, OBI (all funding to UC Regents only). Speaker's Bureau: Genomic health. S.M. Tolaney: Grants/Research Support: Genentech, Pfizer, AstraZeneca, Exelixis, Eli Lilly, Novartis, Merck. V. Dieras: Honoraria: -Consultant: Roche-Genentech, Novartis, Lilly, Pfizer; -Speaker Roche, Novartis, GSK, EISAI, Pfizer; Travel expenses: Roche, Novartis, Pfizer, GSK, EISAI, AstraZeneca. D. Patt: Employee of Texas Oncology, and McKesson Specialty Health. H. Wildiers: Advisor for Eli Lilly and Company. S. Nanda, A. Koustenis: Employee of Eli Lilly and Company, and may hold company stocks. M.N. Dickler: Advisor: Eli Lilly. Consultant: TapImmune, Novartis, Genentech/Roche, AstraZeneca, Pfizer, Syndax, Puma biotechnology, and G1 Therapeutics. Research support: Lilly, Genentech/Roche, and Norvatis. All other authors have declared no conflicts of interest.

250P A global phase III clinical study comparing NK105 and paclitaxel in metastatic or recurrent breast cancer patients

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Background: Paclitaxel (PTX) is a standard chemotherapy drug for metastatic or recurrent breast cancer (m/r BC). However, it presents problems such as hypersensitivity and peripheral sensory neuropathy (PSN). NK105 is a novel nanoparticle drug delivery formulation that encapsulates PTX in polymeric micelles. In a murine model, passive targeting was shown and NK105 accumulated in tumors. We expected NK105 to have similar efficacy and a better safety profile, regarding hypersensitivity and PSN, compared with PTX, considering a past phase II study in gastric cancer patients (pts). This study aimed to verify the non-inferiority of NK105 to PTX in terms of progression-free survival (PFS) in m/r BC pts.

Methods: Eligible pts were randomly assigned at a 1:1 ratio to either the NK105 (N) or PTX (P) arm. NK105 (65 mg/m^2) and PTX (80 mg/m^2) were administered via intravenous infusion weekly for 3 weeks followed by a 1-week rest period until disease progression. Tumor responses were assessed every 6 weeks by RECIST Ver. 1.1. The primary endpoint was PFS, while the secondary endpoints were overall response rate (ORR), overall survival (OS), and safety. PSN was evaluated by CTCAE Ver. 4.03 and FACT/GOG-NTX Ver. 4 (FACT).

Results: From September 2012 to July 2014, 436 pts were randomized and 422 pts were included in the efficacy analysis. The median PFS (95% CI) for the N and P arms was 256 (212–302) and 260 days (211–350), respectively. The adjusted hazard ratio (95% CI) was 1.255 (0.989–1.592), exceeding the set non-inferiority margin. The ORR and median OS for the N and P arms were 31.6% vs. 39.0%, and 950 vs. 1103 days, respectively. Adverse drug reactions occurred in 96.7% pts in the N arm and 98.1% in the P arm. PSN incidences in the N and P arms were 52.8% and 70.0%, respectively and incidence of Grade 3 or more was lower in the N arm than in the P arm pts. Cumulative PSN incidences between the N and P arms were significantly different (P < 0.01) and were favored in the N arm.

Conclusions: The efficacy of 65 mg/m^2 of NK105 could not be verified in terms of non-inferiority of PFS relative to PTX in this study. NK105 safety profile was generally similar to that of PTX, but the NK105 PSN profile was better than that of PTX. NK105 efficacy should be re-evaluated in future studies.

Legal entity responsible for the study: Nippon Kayaku Co., Ltd.

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251P Efficacy and safety of olaparib combined with eribulin in patients with advanced or metastatic triple negative breast cancer (TNBC) previously treated with anthracyclines and taxanes: The final analysis of a Japanese phase I/II trial

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Background: Prognosis of metastatic TNBC is poorer compared with those of other subtypes, because of the lack of effective treatment target. TNBC contains molecularly heterogeneous phenotypes, some of which are influenced by germline (g) *BRCA*1/2 mutation. Eribulin is one of standard treatments for metastatic TNBC and olaparib (Lymparza™), a PARP (poly ADP ribose polymerase) inhibitor, has shown remarkable efficacy in BRCA mutated breast cancer. Therefore, we evaluated the efficacy and safety of the combination of these drugs in a phase I/II trial (UMIN00009498) with an expectation of synergistic effect.

Methods: In phase I, we have determined the recommended dose as 300mg bid of olaparib twice daily and 1.4 mg/m^2 of eribulin intravenously on day 1 and 8 in 21-day cycle. The primary efficacy endpoint in phase II was tumor response rate (RR) in the central review. The planned size was 24, with one-sided alpha of 0.1, power of 0.8, expected RR of 0.3 and threshold of 0.1.

Results: Twenty-four patients were enrolled from June 2014 to December 2014 in phase II. The median age was 46 years old (range: 27 to 73). The median number of prior chemotherapy regimens was 3 (range: 2 to 6). Sixteen patients (66.7%) had visceral metastasis and 8 had non visceral metastasis. Dose intensity of eribulin was 0.69 (mg/m^2-week) and that of olaparib was 2086.2 (mg/week). RR in central review was 29.2% (80%CI: 17.0-44.2), including 7 with PR, 7 with SD, 7 with PD and 3 with NE; thus, the null hypothesis was rejected. In institutional decision, RR was 37.5% (9/24; 95%CI, 18.8-59.4), including1 patient with CR. Median progression-free survival was 4.2 months (95%CI: 3.0 to 7.4). Median overall survival was 14.5 months (95%CI: 4.8 to 22.0). Safety was analyzed separately for phase I and II. Significant severe adverse events (>=G3) were leukocytopenia (87.5%, 83.3%), neutropenia (87.5%, 83.3%), febrile neutropenia (20.8%, 33.3%), anemia (16.7%, 41.7%) and thrombosis (0%, 8.3%), respectively.

Conclusions: The combination of olaparib and eribulin was well tolerated and showed a promising efficacy and safety for metastatic TNBC.

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Legal entity responsible for the study: National Cancer Hospital () National Cancer Center National Cancer Center

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252P Phase II study of gemcitabine, trastuzumab, and pertuzumab for HER2-positive metastatic breast cancer after prior pertuzumab-based therapy

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Background: The combination of taxanes with trastuzumab (H) and pertuzumab (P) for first line treatment of HER2-positive metastatic breast cancer (MBC) is associated with improved progression-free (PFS) and overall survival (OS). Treatment per physician's choice with anti-HER2 therapy after second line therapy is associated with a median PFS of 3 months. While continued use of H in therapeutic combinations after progression on H-based therapy is standard, the efficacy of continuing HP-based treatment after progression on P-based therapy is unknown.

Methods: This is a single arm phase II trial of gemcitabine (G) with HP. Eligible patients (pts) had HER2-positive (IHC 3+ or FISH $\geq$ 2.0) MBC with prior HP-based treatment and $\leq$ 3 prior chemotherapies. Pts received G (1200 mg/m^2) on days 1 and 8 of a q 3 week (w) cycle, and H (8 mg/kg load $\rightarrow$ 6 mg/kg) and P (840 mg load $\rightarrow$ 420 mg) q3w. The primary endpoint is PFS at 3 months. Secondary endpoints include OS, safety and tolerability. An exploratory endpoint is to compare PFS by RECIST criteria versus 18-F FDG-PET response criteria. The study therapy will be considered successful if at least 27/45 (60%) patients are progression free at 3 months.

Results: As of 27 April 2017, 45 of 45 pts are enrolled; 39 are evaluable at 3 months and 6 have not had 3-month evaluation. At 3 months, 30/39 (77%) are progression free (1 CR, 8 PR, 21 SD); 9 pts progressed. There are no cardiac or febrile neutropenic events to date. 4 pts required G dose reduction (3 grade 3 neutropenia and 1 grade 3 vomiting) and the study was amended to lower initial G dose to 1000 mg/m^2.

Conclusions: The preliminary 3 month-PFS is 77% in evaluable pts (95% CI 62% to 87%). The updated 3 month-PFS results will be presented. Continuation of P beyond progression is associated with apparent clinical benefit. A randomized trial is justified to confirm this clinically important observation.

Clinical trial identification: NCT02252887

Legal entity responsible for the study: Memorial Sloan Kettering Cancer Center

Funding: Genentech/Roche

Disclosure: All authors have declared no conflicts of interest.

253P Abemaciclib plus fulvestrant in patients (pts) with HR+/HER2- endocrine therapy naïve (EN) advanced breast cancer - an exploratory analysis of MONARCH 2

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Background: MONARCH 2 demonstrated that the addition of abemaciclib, dosed on a continuous schedule at 150 mg twice daily, to fulvestrant (F) significantly improved progression-free survival (PFS) and objective response rate (ORR) compared to placebo (P) plus F (PFS hazard ratio [HR], 0.553, P<.0000001; ORR in measurable disease 48.1% vs 21.3%, P<.001) in women with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) advanced breast cancer (ABC) who had progressed on endocrine therapy (ET). Here we present efficacy and safety findings from an exploratory cohort of EN pts from MONARCH 2 not included in the intent-to-treat (ITT) population.

Methods: Pts were randomized 2:1 to receive abemaciclib or P + F (500 mg, per label). Pre/perimenopausal women received a gonadotropin-releasing hormone agonist. Pts were not allowed to have had chemotherapy in the advanced setting. Pts were stratified by metastatic site (visceral, bone only, other). The primary endpoint for this analysis was investigator-assessed PFS which was described using the Kaplan-Meier method and a Cox model.

Results: Forty-four EN pts were randomized to abemaciclib + F (N = 28) or P + F (N = 16). 46% of pts presented with visceral disease, 77% with measurable disease, and 82% were postmenopausal. At the time of the analysis, 18 pts were still on treatment (13 [46.4%] in the abemaciclib + F arm and 5 [31.3%] in the P + F arm). 18 PFS events were observed (9 [32.1%] in the abemaciclib + F arm and 9 [56.3%] in the P + F arm). The median PFS had not been reached in the abemaciclib + F arm and was 23.1 months in the P + F arm (stratified HR, 0.454; 95% CI: 0.179, 1.154). The ORR in pts with measurable disease was 60.0% (5% complete response [CR]) in the abemaciclib + F arm and 57.1% (0% CR) in the P + F arm. The most common adverse events were diarrhea, nausea, fatigue,

and neutropenia. Diarrhea generally occurred in the early cycles and was managed with dose adjustment and conventional anti-diarrheal medication.

Conclusions: In this exploratory cohort of EN pts, the addition of abemaciclib to fulvestrant demonstrated a comparable increase in PFS and consistent safety results to those observed in the ITT population in MONARCH 2.

Clinical trial identification: NCT02107703

Legal entity responsible for the study: Eli Lilly and Company

Funding: Eli Lilly and Company

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254P Matching-adjusted indirect treatment comparison of ribociclib and palbociclib as first-line treatments for HR+, HER2– ABC

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Background: Ribociclib (RIB) and palbociclib (PAL) combinations with letrozole (LET) vs LET alone have been evaluated in separate Phase 3 randomized controlled trials in patients with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2–) advanced breast cancer (ABC); however, no head-to-head comparative studies have been conducted. Classic indirect treatment comparison (ITC) can lead to biased results due to differences in patient populations and trial designs. These differences can be corrected by using the matching-adjusted indirect comparisons (MAIC) technique. Here, we compare RIB and PAL in patients with HR+, HER2– ABC using MAIC.

Methods: Individual patient data were available for the RIB trial (MONALEESA-2). As only published summary data were available for the PAL trial (PALOMA-2), RIB data were adjusted to closely match the PAL data. Data for RIB-treated patients were assigned weights so that weighted mean baseline characteristics matched those reported for PAL. Overall survival data have not been reported for PALOMA-2, thus only progression-free survival (PFS) data were compared. Adjusted hazard ratios (HRs) for PFS were calculated using weighted Cox regression models and used to calculate indirect HRs with 95% confidence intervals (CIs). Classic frequentist ITC was performed before and after adjustment. ITC of Grade 3/4 adverse events (AEs) was also performed.

Results: The unadjusted PFS HR (95% CI) for RIB+LET vs LET was 0.556 (0.429; 0.721) and for PAL+LET vs LET was 0.580 (0.460; 0.720). MAIC adjustment for age, race, region, Eastern Cooperative Oncology Group status, disease stage at diagnoses, sites of metastases, and chemotherapy setting at baseline provided a RIB+LET vs LET HR estimate of 0.501 (0.365; 0.688). The HR for unadjusted ITC of RIB vs PAL was 0.959 (0.681; 1.350) and by MAIC was 0.864 (0.586; 1.274). ITC of Grade 3/4 AEs yielded a risk ratio (RR) of 0.81 (0.61; 1.08) for RIB vs PAL.

Conclusions: Using MAIC methodology due to a lack of head-to-head trials, the resulting HRs for PFS were comparable. Similarly, using ITC, AE profiles were also comparable although the RR for AEs slightly favored RIB.

Legal entity responsible for the study: Novartis Pharmaceuticals Corporation

Funding: Novartis Pharmaceuticals Corporation

Disclosure: A. Forsythe: Consultant for Novartis. D. Chandiwana, M. Monaco: Novartis employee and stocks/shares. All other authors have declared no conflicts of interest.

255P Phase 1 dose-escalation study of single-agent ZW25, a HER2-targeted bispecific antibody, in patients (pts) with HER2-expressing cancers

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Background: HER2 is expressed on many cancers (ca) at varying levels. ZW25, a novel bispecific antibody, targets the same HER2 domains as trastuzumab (T) and pertuzumab (P). In preclinical studies ZW25 shows increased binding, internalization and anti-tumor activity relative to T in models of low to high HER2.

Methods: 3 + 3 dose escalation study in pts with HER2 IHC 1-3+ or FISH+ ca, who have progressed after standard treatment (tx) including HER2 targeted agents, and have measurable or non-measureable disease per RECIST 1.1. ZW25 was given weekly (QW; 5, 10 or 15 mg/kg) or biweekly (Q2W; 20 mg/kg) in 4 week cycles. Assessments included HER2 status (local and central read), adverse events (AEs), tumor response, PET scan, immunogenicity and PK.

Results: 16 pts (8 breast; 6 gastric/esophageal ≥; 1 colorectal [CRC]; 1 adnexal) have received ZW25 QW at 5 (n = 3), 10 (n = 6) and 15 mg/kg (n = 7); 20 mg/kg Q2W is enrolling. All pts had prior T; breast ca pts also had T-DM1 (n = 8), P (n = 6) or lapatinib (L; n = 6). 12 pts had IHC 3+/FISH+ ca (local and central read); 1 CRC ca was HER2 heterogeneous (IHC 3+/FISH+ and IHC 0/FISH -), and 3 GE were IHC 1 + (central read). No dose limiting toxicities were observed. The most common AEs were Diarrhea (44%, all grade 1), Infusion reaction (IR) (44%, grade 1 and 2), and Fatigue (31%). PK was non-linear and increased with dose of ZW25. 8/13 pts tested had anti-drug antibodies (ADA) at baseline. No increases in titers and no new detectable ADA were seen. In 7 breast ca pts (1 too early), best overall response (BoR) was 2 PR (both 10 mg with prior T, P, T-DM1, L); 2 SD (>8 cycles in 5 mg pt with prior T, P, T-DM1; >2 cycles in 15 mg pt, with T, P, T-DM1, L); and 3 PD. BoR in 5 GE pts (1 too early): 1 SD > 4 cycles (10 mg, prior T, IHC 3+) and 4 PD. BoR in adnexal (10 mg) and CRC (15 mg) pts was PD.

Conclusions: ZW25 was well tolerated with promising single-agent activity including SD > 6 mo and PR in pts with HER2 expressing ca who have progressed after standard tx, including multiple lines of prior HER2 targeted agents. These early signs of activity support the therapeutic potential of ZW25.

Clinical trial identification: NCT02892123

Legal entity responsible for the study: Zymeworks Inc

Funding: Zymeworks Inc

Disclosure: M. Beeram, D. Rasco: Employee of START. D. Hausman: Stockholder and employee Zymeworks Biopharmaceuticals Inc. R. Korn: Employee and leadership role at Imaging Endpoints. G. Rowse: Employee of Zymeworks Inc. J. Thimmarayappa: Employee of Zymeworks Biopharmaceuticals Inc. A. Tolcher: Employee of START, leadership role at Symphogen, member of Zymeworks Clinical Advisory Board. F. Meric-Bernstam: Honoraria: Genentech, Roche Diagnostics. Consulting or Advisory Role: Celgene, Genentech, Inflection Biosciences, Novartis, Roche. All other authors have declared no conflicts of interest.

256P Efficacy of palbociclib plus fulvestrant in advanced Hormone Receptor-positive (HR+) metastatic breast cancer (MBC) pretreated with everolimus: Real-life data from the french temporary authorization for use (TAU) at the Institut de Cancérologie de l'Ouest

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Background: The CDK4-6 inhibitor palbociclib, combined with hormonal therapy is a new standard of treatment for HR+ Metastatic Breast Cancer. Before the European Medicines Agency approval, a Temporary Authorization for Use (TAU) has been set up in France restricted to patients pretreated with everolimus. We present the efficacy data of this combination in this population.

Methods: Between November 2015 and November 2016, all the patients treated with palbociclib + fulvestrant according to the TAU in our institution were prospectively included. Datas from their medical records and adverse events (AE) were collected.

Results: 60 patients received at least one dose of palbociclib in combination with fulvestrant with a median age of 61 years. 50 patients (83.3%) had visceral metastasis and 10 (16.7%) had bone only disease. Patients had received an average of 5.3 lines of treatment before palbociclib initiation, including hormonal therapy (mean = 3.0) and chemotherapy (mean = 2.3). Of note, 28 patients (46.7%) had received fulvestrant previously and all had been pretreated with everolimus. With a median follow-up of 8.1 months, median progression free survival (PFS) was 6.1 months (95% CI, 4.2 to 7.4) and median overall survival was not reached. PFS was the same according to the presence of visceral metastasis or no (HR 1.46 (95% CI, 0.57 to 3.74), p = 0.42). Interestingly, patients treated previously with fulvestrant and subsequently re-challenged with fulvestrant and palbociclib had a PFS of 6.4 months, which was similar to patients who didn't receive fulvestrant previously (HR = 1.00 (95% CI 0.55 to 1.83), p = 1.00). The most common AE were neutropenia (n = 53), thrombocytopenia (n = 25) and anemia (n = 20). At the time of this analysis (April 2017), 36 patients received a further line of treatment after progression.

Conclusions: In this heavily pretreated population, the association of fulvestrant plus palbociclib provides an interesting median PFS of 6.1 months. Patients previously treated with fulvestrant seem to derive the same magnitude of benefit compared to fulvestrant naive patients.

Legal entity responsible for the study: Institut de Cancérologie de l'Ouest

Funding: None

Disclosure: All authors have declared no conflicts of interest.

257P A phase 1 study of BYL719, an α-isoform selective PI3K inhibitor, in Japanese patients with advanced solid malignancies

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Background: BYL719 is an oral inhibitor that selectively targets the α-isoform of class l PI3K. In a first-in-human ph1 study in mostly Western patients (pts) with *PIK3CA* alteration, the maximum tolerated dose for once-daily (qd) BYL719 was declared as 400 mg and preliminary antitumor activity was observed. Previous preliminary findings showed tolerability, safety, and pharmacokinetic (PK) results in dose escalation of the first-in-Japanese ph1 study. Here, we report results of the food effect on the PK profile of BYL719 at steady state, additional safety, and preliminary efficacy in Japanese pts.

Methods: Pts were aged ≥18 years with histologically confirmed, advanced solid tumors. Pts received BYL719 qd in 28-day cycles until disease progression, unacceptable toxicity, or investigator/pts decision. The objectives in the expansion part were to assess food effect on PK profile, preliminary antitumor activity, and safety. Pts with PIK3CA alteration were selected in the expansion part and were randomized to receive BYL719 at the recommended dose 350 mg qd in fasted or fed condition on cycle 1 day 22 and cycle 2 day 1 in a crossover fashion. Pts received BYL719 ∼1 hr following a light breakfast and continued to be fasted for 1 hr after each dose.

Results: Thirty-three pts were enrolled and all pts discontinued treatment. The median duration of exposure was 71.0 days (range, 6-462). The common BYL719-related all-grade (Gr) AEs (>30%) were hyperglycemia, rash maculopapular (48.5%, each), diarrhea (45.5%), and decreased appetite (33.3%). BYL719-related Gr 3 or 4 AEs (≥20%) were rash maculopapular (24.2%) and hyperglycemia (21.2%). Eight pts were enrolled in the expansion part; six of them were eligible for PK analysis. The geometric mean values of dose-normalized C_{max} and $AUC_{0\text{-}24}$ in fed state were 78% and 56% higher than those in fasted state, respectively. One pt experienced Gr 4-infected neoplasm meeting DLT criteria, 1 pt with uterus cancer and *PIK3CA* mutation had an unconfirmed partial response, and 18 pts had a stable disease.

Conclusions: In this ph1 study of BYL719 in Japanese pts, a positive food effect and preliminary antitumor activity were observed at steady state in pts with *PIK3CA* mutation status.

Clinical trial identification: NCT01387321

Legal entity responsible for the study: Novartis Pharmaceuticals KK, Tokyo, Japan

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258P Phase 1 study of RX-5902, a novel orally bioavailable inhibitor of phosphorylated P68, which prevents β-catenin translocation in advanced solid tumors

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Background: RX-5902 is a novel compound that targets phosphorylated p68 RNA helicase (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 through inhibition of β-catenin translocation. We report preliminary results of the Phase 1 study of RX-5902 as a single agent to treat advanced solid tumors.

Methods: The dose finding portion of the Phase 1 study (NCT02003092) was designed to evaluate safety, tolerability and dose limiting toxicities, to identify the maximum tolerated dose and a recommended phase 2 dose and schedule (RP2D). Secondary objectives were pharmacokinetics (PK) and antitumor activity (RECIST v1.1). Eligible subjects (aged ≥ 18 years), with relapsed/refractory solid tumors that had been heavily pretreated, received oral RX-5902 ranging from 25 mg to 350 mg and administered at 1, 3, 5 or 7 times per week for 3 weeks followed by 1 week of rest or for 4 weeks without rest.

Results: As of May 2017, 35 subjects (23 Females, 12 males) were treated with oral RX-5902. The dose limiting toxicities were G4 hyponatremia (n = 1) and G3 fatigue (n = 1) at 300 mg administered daily for 4 weeks. The maximum tolerated dose of 250 mg, will be studied further in the Phase 2a portion. Of the 35 subjects treated, 15 subjects (breast ER+/PR+/Her2-, triple negative breast (n = 2), cervical (n = 2), neuroendocrine (n = 3), paraganglioma, colorectal (N = 3), pancreatic, ovarian, head and neck cancers) experienced stable disease; 2 subjects have received treatment for > 2.5 years. The most common related adverse events were G1/G2 anorexia, G1/G2 nausea, G1/G2 vomiting, G1/G2 diarrhea, G1 weight loss and G1/G2 fatigue. Oral RX-5902 was bioavailable with median T_{max} of 2 hours and median elimination half-life of 12 hours.

Conclusions: Data from this study support that RX-5902 is safe and well-tolerated at the doses and schedules tested. The RP2D of 250 mg of RX-5902 administered daily for 5 consecutive days for 4 weeks is being studied further in metastatic triple negative breast cancer in the Phase 2 portion of this study.

Clinical trial identification: NCT02003092

Legal entity responsible for the study: Rexahn Pharmaceuticals, Inc.

Funding: Rexahn Pharmaceuticals, Inc

Disclosure: C. Peterson, R. Pila, E. Benaim: Employee of Rexahn Pharmaceuticals, Inc. All other authors have declared no conflicts of interest.

259P Adherence to International ESO-ESMO (ABC) guide-lines in HER2-ve metastatic breast cancer (MBC) patients (pts): Preliminary results of the GIM 13 - AMBRA Study

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Background: ESO/ESMO develops consensus guidelines for MBC treatment every 2 years, potentially applicable worldwide. Aim of the present analysis is to verify the adherence to ABC recommendations for HER2-ve MBC in the context of the AMBRA study.

Methods: AMBRA is a longitudinal cohort study, aiming to describe the choice of first and subsequent lines of treatment in HER2-ve MBC pts receiving at least one Chemotherapy (CHT) (SABCS 2016, P5-15-07 & P5-14-09). For the present analysis, we selected 4 statements from the ABC1 & ABC2 Conferences, comparing them with the clinical choices of 1st-line therapy in all evaluable cases.

Results: So far, 791 pts have been enrolled, of whom 586 (74.1%) have received CHT as 1st-line treatment. 479 pts (81.7%) had Luminal tumours at diagnosis. First-line CHT was monotherapy in 89 pts (25.2%), anthra-based CHT in 45 (7.7%) and platinum-based in 38 (6.5%), mainly TNBC (20/38, 52.6%). Selected recommendations and percentages of adherence are reported in Table.

Conclusions: The adherence to clinical recommendations is very low, being only partially applied in all the clinical situations analyzed. Educational interventions are urgently needed and a confrontation with the clinical community is strongly recommended.

Table: 259P Adherence to ABC recommendations for HER2-ve pts

	n/N (%of adherence)	
1 - Anthracycline (A)- or Taxane (T)-based regimens, preferably as a single agent, would usually be considered as first-line CHT, in those pts who have not received these regimens as adjuvant treatment	A/T mono 59/270 (21.8%) A/T poly 101/270 37.4%)	160/270 (59.2%)
2 - In pts with taxane-naive and anthracycline-resistant MBC, taxane-based therapy, preferably as a single agent, would usually be considered as the treatment of choice	T mono 89/431 (20.6%) T poly 119/431 (27.6%)	208/431 (48.2%)
3 - Other options are Capecitabine and Vinorelbine	135/586 (23.0%)	
4 - If given in the adjuvant setting, a taxane can be re-used in the metastatic setting, particularly if there has been at least 1 year of disease-free survival	DFI > 12 months 74/79 (93.7%) DFI </= 12 months 5/79 (6.3%)	79/151 (52.3%)

Legal entity responsible for the study: Marina E. Cazzaniga

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Disclosure: All authors have declared no conflicts of interest.

260P M-bioscore: A practical tool for predicting outcomes among patients with previously untreated metastatic breast cancer

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Background: Two prognostic models "bioscore" and "Neo-bioscore" were recently published and validated to help predict the outcomes of patients with non-metastatic breast cancer treated with either upfront surgery or upfront neoadjuvant chemotherapy. A comparable model for metastatic disease is yet to be developed. The current study thus sought to propose and validate a third model "M-bioscore" to help predict the outcomes of treatment-naïve patients with metastatic breast cancer.

Methods: Through SEER*Stat program, surveillance, epidemiology and end results (SEER) database (2010-2013) was accessed. The resulting cohort was equally split into two halves: training set (to guide model development) and validation set (to test the model prediction). Multivariate analysis for the candidate prognostic factors (extent of metastases, estrogen receptor (ER), progesterone receptor (PR), HER2 neu and nuclear grade) was conducted through a Cox proportional model. M-bioscore was then calculated for each patient. Cancer-specific survival analyses according to M-bioscore were conducted through Kaplan-Meier analysis/log-rank testing.

Results: A total of 6655 patients with previously untreated metastatic breast cancer and complete data were identified in the period from 2010-2013. The following factors were associated with better cancer-specific survival in multivariate analysis in the training set (isolated distant nodal metastases, ER positivity, PR positivity, HER 2 neu positivity and lower nuclear grade) ($P < 0.01$). This has been shown for both training and validation sets. accordingly, the M-bioscore model has been proposed as follows: an M-bioscore point is given for each of ER negativity, PR negativity, HER2 neu negativity and nuclear grade 3. The site/distribution of metastasis are given the following points: 0 for isolated distant lymph nodes, 1 for isolated bone/skin deposits, 2 for isolated liver/lung deposits, 3 for isolated brain deposits or multiple sites of metastases. A total M-bioscore was then calculated for each case in the training cohort (which may range from 0 to 7). After assignment of a total M-bioscore for each patient, cancer-specific survival was compared according to the score. Log rank testing with pair wise comparisons between all different scores was conducted. For cancer-specific survival assessment according to the M-bioscore, *P* values for pair wise comparisons among different score points were significant ($P < 0.05$) except for the comparison between score 0 and score 1/score 2/score 3 in the training cohort. These findings have been confirmed in the validation and overall cohorts. Table shows the three year cancer-specific survival (CSS) rates for patients in the overall cohort according to M-bioscore.

Conclusions: M-bioscore is a novel, easy and reliable tool for predicting the outcomes of patients with previously untreated metastatic breast cancer. Further external validation within the context of other population-based cohorts is recommended.

Legal entity responsible for the study: Omar Abdel-Rahman

Table: 260P Three-year cancer-speci˚c survival according to M-bioscore

M-bioscore	All patients	
	N (%)	CSS rate
0	22 (0.3%)	95%
1	273 (4.1%)	81%
2	1567 (23.5%)	69%
3	1202 (18.1%)	60%
4	1680 (25.2%)	52%
5	1038 (15.6%)	35%
6	590 (8.9%)	26%
7	283 (4.3%)	17%

Funding: None

Disclosure: All authors have declared no conflicts of interest.

261P Is PFS a more relevant endpoint than OS in 1L HR+, HER2– MBC? A systematic literature review

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Background: Hormone receptor-positive (HR+), human epidermal growth factor 2 receptor-negative (HER2–) metastatic breast cancer (MBC) accounts for 73% of all MBC.[1] Endocrine therapy (ET) is the basis of first-line (1L) therapy for patients (pts) with HR+, HER2– MBC; however, efficacy is limited by ET resistance. Novel therapies have demonstrated improvements in progression-free survival (PFS) vs standard ET. The clinical relevance of PFS is debated due to a lack of direct correlation with overall survival (OS) benefit, and cases of asymptomatic progression. We review studies of HR+ HER2– MBC to assess factors that influence OS and treatment response, and changes in health-related quality of life (HRQoL).

Methods: The Embase®, MEDLINE®, and Cochrane databases were systematically searched to identify studies in adult women with HR+, HER2– MBC, published 2006–January 2017, and written in English. Phase (Ph) 2 and 3 randomized controlled-trials (RCTs), observational, and retrospective studies were considered and HRQoL and real-world evidence reviewed.

Results: 79 RCTs were identified: 58 (73%) in the 1L setting and 21 (27%) in the ≥second-line setting. PFS data were reported in 61 (77%) studies; 31 (51%) reported significant PFS improvement. OS was reported in 44 (56%) of studies; only 11 (14%) reported a significant OS improvement. Significant improvements in both PFS and OS were reported in only 6 (8%) studies (1 Ph 2; 5 Ph 3). Pts with HER2– MBC received on average ≥5 lines of therapy, with no defined treatment pathway. Baseline characteristics, prior therapies, and the type and number of post-progression therapies significantly impacted OS. PFS, response rates, and HRQoL decreased with each line of therapy (EQ-5D: 0.78 1L vs 0.70 post-progression).

Conclusions: Multiple HR+, HER2– MBC therapies have been investigated yet few CTs have achieved a significant improvement in OS. Multiple factors besides the choice of 1L therapy impact OS, such as post-progression therapies, which cannot be controlled in RCTs. This study emphasizes the importance of PFS improvement coupled with HRQoL maintenance in 1L treatment of HR+, HER2– MBC. 1. Howlader N *et al. J Natl Cancer Inst* 2014;106:dju055.

Legal entity responsible for the study: Novartis Pharmaceuticals Corporation

Funding: Novartis Pharmaceuticals Corporation

Disclosure: A. Forsythe: Consultant for Novartis. D. Chandiwana, M. Thabane, J. Baeck: Novartis employee and Novartis stocks/shares. J. Barth: Novartis employee. All other authors have declared no conflicts of interest.

262P PFS/TTP as a potential surrogate for OS in HR+, HER2– MBC

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Background: Several, recent randomized controlled trials (RCTs) in hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2–) metastatic breast cancer (MBC) have demonstrated a significant improvement in

progression-free survival (PFS); however, few have reported an improvement in overall survival (OS). OS may be an imperfect endpoint due to the impact of factors such as baseline characteristics and subsequent therapies. Investigation of the use of PFS or time to progression (TTP) as a surrogate for OS in HR+, HER2– MBC has been limited. This study assesses the correlation of PFS/TTP and OS in HR+, HER2– MBC across all lines of therapy.

Methods: A systematic literature review of RCTs in HR+, HER2– MBC was conducted to identify studies that reported both median PFS/TTP and OS. The correlation between PFS/TTP and OS was evaluated using Pearson's product-moment correlation and Spearman's rank correlation. Subgroup analyses were performed to explore possible reasons for heterogeneity. Errors-in-variables weighted least squares regression (LSR) was used to model incremental OS months as a function of incremental PFS/TTP months. An exploratory analysis investigated the impact of 3 covariates (chemotherapy vs other, PFS vs TTP, and 1L vs > 1L) on the use of PFS/TTP in OS prediction. The lower 95% prediction band was used to determine the minimum incremental PFS/TTP months below which there would be no predicted OS benefit (the surrogate threshold effect [STE]).

Results: A total of 39 studies were identified. There was a statistically significant correlation between median PFS/TTP and OS (Pearson=0.741, $p < 0.000$; Spearman=0.650, $p < 0.000$). Results were unchanged for chemotherapy and hormonal or targeted therapy, and for line of therapy. Initial LSR analysis yielded an R^2 of 0.354; 1 PFS/TTP month corresponded to 1.13 OS months. The addition of 3 covariates improved R^2 to 0.569; 1 PFS/TTP month corresponded to 0.78 OS months. The STE for OS benefit was 5–6 months of incremental PFS/TTP.

Conclusions: Results of this study indicate a significant association between PFS/TTP and OS, which may justify the use of PFS/TTP as surrogate for OS benefit during regulatory approval and subsequent reimbursement of new therapies in HR+, HER2– MBC.

Legal entity responsible for the study: Novartis Pharmaceuticals Corporation

Funding: Novartis Pharmaceuticals Corporation

Disclosure: A. Forsythe: Consultant for Novartis. D. Chandiwana, M. Thabane, J. Baeck: Novartis employee and Novartis stocks/shares. J. Barth: Novartis employee. All other authors have declared no conflicts of interest.

263P Survival gains from advances in first-line systemic therapy for HER2-positive metastatic breast cancer in the U.S., 1995-2015

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Background: Of the approximately 67,000 women diagnosed with metastatic breast cancer (mBC) annually in the U.S., nearly 10,700 are HER2-positive (HER2+). Prior to the advent of HER2 targeted therapy, women with HER2+ mBC had a less favorable prognosis than those with HER2-negative mBC. The objective of this study was to quantify survival gains for women with HER2+ mBC from 1995-2015, a period spanning pre HER2 targeted therapy to the present, where multiple targeted therapies are available.

Methods: We developed a simulation model to estimate overall survival (OS) for successive cohorts diagnosed with HER2+ mBC from 1995-2015. OS data were derived from clinical trials referenced in NCCN guidelines and extrapolated to a lifetime horizon by fitting Weibull curves. Patients were assigned to regimens in each diagnosis year using information from the IPSOS 'Global Oncology Monitor'- a commercial treatment registry. Results were calibrated with SEER OS data. Outcomes included 5-year OS, expected OS, and total life years (LYs) for all patients with HER2+ mBC. Annual incidence of HER2+ mBC was assumed to be constant over time.

Results: Over the period 1995-2015, expected 5-year OS for women with HER2+ mBC increased by 28.9%. Mean expected per-patient OS improved by 28.1 months (25,000 population LYs) (see Table). The largest gain (15.7 months) occurred between 2010 and 2015–the period over which pertuzumab-based treatment was approved for first-line use and gained substantial market penetration. The smallest gain (2.4 months) occurred between 1995 and 2000—the period over which trastuzumab-based treatment was approved, but had not yet achieved market penetration.

Conclusions: The introduction and expanded use of targeted treatments, along with other advances in care, have provided substantial individual- and population-level survival gains for women with HER2+ mBC. A considerable proportion of the expected OS differences between 1995 and 2015 took place after the introduction and uptake of trastuzumab and pertuzumab-based regimens.

Table: 263P

Diagnosis Year	5-Year OS (%)	Mean Per-Patient OS (Months)	Population Life Years
2015	38.8	55.3	49300
1995	9.9	27.2	24300
Difference	+28.9	+28.1	+25000

Legal entity responsible for the study: Genentech

Funding: Genentech

Disclosure: J. Roth, S. Sullivan, S. Ramsey: Research funding from Genentech, Inc. P. Bajaj, C. Reyes, V. Antao, A. Stein: Employee of Genentech, Inc; Stock Ownership in Roche. R. Mahtani: Advisory boards for Genentech, Pfizer, Amgen, Celgene, Sandoz; Research support from Genentech.

264P Progression-free survival (PFS) and site of first progression in HER2+ metastatic breast cancer (MBC) patients (pts) with (w) or without (w/o) brain metastases: A pooled analysis of tucatinib phase I studies

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Background: Brain metastases (BM) are frequent in HER2+ MBC occurring in > 30% of pts and are associated w significant neurologic morbidity and mortality. Current treatment strategies for BM primarily utilize radiotherapy (RT) and in selected instances surgical resection. Tucatinib is a highly selective oral HER2+ tyrosine kinase inhibitor that has shown promising results in HER2+ MBC both in pts w and w/o BM.

Methods: Two Phase 1b studies of tucatinib were pooled to compare PFS and sites of relapse in pts w or w/o BM.

Results: 77 pts were analyzed, all treated at the recommended Phase 2 dose of 300mg PO BID of tucatinib, 50 in the 004 trial (tucatinib + T-DM1) and 27 in the 005 trial (tucatinib + trastuzumab + capecitabine). All pts were heavily pretreated w a median of 3 prior therapies including a taxane, trastuzumab, pertuzumab, T-DM1 and lapatinib. Four cohorts of pts were identified: 46% (35) had systemic metastases only, 17% (13) had previously treated (RT w or w/o surgery) and stable BM, 19% (15) had previously treated and progressive BM and 17% (13) had asymptomatic untreated BM demonstrated by screening MRI. Median PFS across cohorts was 8.5, 6.1, 9.0 and 7.1 months, respectively. No statistically significant difference in PFS was seen when comparing the non-BM cohort to all BM cohorts (median of 8.5 vs. 6.7 months; $p = 0.65$). The risk of progression in brain in pts w baseline BM was 48.8% overall (41.5% in brain only; 7.3% in brain and body) compared to an 11.1% overall (8.3% in brain only; 2.8% in brain and body) in pts w/o baseline BM.

Conclusions: 54% of pts entered tucatinib studies w baseline BM, either previously treated (stable or progressive) or untreated. The cohorts of pts analyzed appear to differ only in the site of disease progression. Although pts w/o baseline BM primarily have progression in extraneural sites and pts w baseline BM primarily have progression in the CNS, PFS is comparable across cohorts. Furthermore, pts both w and w/o BM have durable responses w these combination therapies following multiple lines of prior HER2 targeted therapy. These data support the use of tucatinib in both pts w and w/o BM in the accruing HER2CLIMB trial.

Clinical trial identification: ONT-380-004 and ONT-380-005

Legal entity responsible for the study: Cascadian Therapeutics, Inc.

Funding: Cascadian Therapeutics, Inc.

Disclosure: All authors have declared no conflicts of interest.

265P Survival of patients with aromatase inhibitors sensitive, HR+/HER2- metastatic breast cancer treated with a first-line endocrine therapy or chemotherapy in a multicenter national observational study

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Background: For HR+/HER2– metastatic breast cancer (mBC), international guidelines recommend the use of endocrine therapy (ET) as first-line (L1) treatment except in case of "visceral crisis" for which chemotherapy (CT) is advised. Few studies directly compare these two treatment options. In 2014, UNICANCER launched the Epidemiological Strategy and Medical Economics (ESME) Research program to centralize real-world data in oncology. We sought to use this database to study this question.

Methods: All patients (pts) who initiated treatment for a newly diagnosed mBC between January 2008 and December 2014 in all 18 French Comprehensive Cancer Centers were included in the ESME mBC database. ESME Research program centralized all existing data using retrospective data collection. Primary endpoint of the present study was progression free survival (PFS1) and overall survival (OS) according to L1 treatment for aromatase inhibitors sensitive (AIS) HR+/HER2- mBC pts.

Results: 6265 pts out of 16703 in ESME, had AIS HR+/HER2- mBC. As L1 therapy, 2733 pts (43.6%) received ET alone, while 3532 received CT (56.4%). Among these 3532 pts, 2073 (58.7%) received ET as maintenance treatment after CT. A Cox multivariate analysis with significant prognostic variables identified a lower risk of death in the patients with L1 ET (HR = 0.839, 95% IC [0.772-0.911], $p < 0.0001$). Patients receiving CT were younger (median age 56.0 *vs* 66.0, $p < 0.001$), more likely to have visceral metastasis (61.6% *vs* 40.1%, $p < 0.001$) and SBR III primary tumors (31.3% vs 18.8%, $p < 0.001$). Median PFS1 was 15.18 months for L1 ET (95% CI, 14.45-16.20) *vs* 12.58 months for L1 CT +/- hormone maintenance (95% CI, 11.89-13.14), $p < 0.0001$. Median OS was 60.78 months for L1 ET (95% CI, 57.16-64.09) *vs* 49.64 months for L1 CT (95% CI, 47.31-51.64), $p < 0.0001$.

Conclusions: The results show that despite guidelines, a majority of AIS HR+/HER2- mBC pts still received CT as first-line treatment in the past years. PFS1 and OS data do not suggest any advantage of this aggressive strategy over ET alone. Advanced statistical methods using the propensity score will be presented in order to control for potential selection bias.

Legal entity responsible for the study: UNICANCER

Funding: UNICANCER

Disclosure: All authors have declared no conflicts of interest.

266P Use of everolimus in advanced hormone receptor positive metastatic breast cancer in a multicenter national observational study

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Background: The everolimus-exemestane combination has been included in the International guidelines for advanced HR+ breast cancer (mBC) since the results of the Bolero-2 trial. Marketing authorization has been granted in France in July 2012. We evaluated the incidence and indication of everolimus (EVE) use before and after marketing authorization and reimbursement.

Methods: All patients who initiated treatment for a newly diagnosed mBC between 01/2008 and 12/2015 in all 18 French Comprehensive Cancer Centers have been included in the real life ESME database, which collects retrospective data using a clinical trial-like methodology.

Results: The ESME program included a total of 16,703 patients of which 9,921 had HR+/HER2- mBC. Median age at metastatic diagnosis was 62.0 year (range 23-96). Visceral metastases were present in 60.3% of cases. Only 4123 patients (41.6%) received endocrine therapy alone as first-line therapy, and 60% were deemed endocrine resistant. Overall, 1,217 (12.3%) pts have received EVE during therapy as of Dec. 2015 (all lines). EVE was given as first line therapy in 117 pts (10% of all EVE pts and 1.2% of pts receiving a first line therapy). In 99/117 pts (85%) EVE was combined with exemestane. Before 2012, EVE was used within clinical trials. After 2012, use of EVE increased steadily. Percentages in the Table refer to the total of pts who received any kind of treatment during a given year of observation (eg 506 pts took EVE in 2015 out of 4435). Median duration of EVE use was 6.0 months (range 0-65) as first line treatment and 3.9 months (range 0-65) in pretreated patients. Patient population and causes of EVE cessation will be detailed at the meeting.

Table: 266P

Year	2008	2009	2010	2011	2012	2013	2014	2015
N	4	7	13	11	133	391	493	506
%	0.20	0.22	0.30	0.21	2.3	6.6	8.6	11.41

Conclusions: In this very large French national and representative cohort of HR+ HER2- mBC, EVE use rose quickly as soon as marketed. EVE was mostly used in pretreated mBC albeit in probably too advanced pts. These data underline the need for physician and patient education for oral therapies.

Legal entity responsible for the study: UNICANCER R&D

Funding: UNICANCER

Disclosure: All authors have declared no conflicts of interest.

267P Can contemporary trials in HER2-negative metastatic breast cancer (mBC) detect overall survival (OS) benefit?

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Background: Although several recent trials have demonstrated improved progression-free survival (PFS) or time to progression (TTP) with first-line regimens for HER2-negative mBC, OS benefit is often elusive. We calculated required sample sizes to power for OS based on published data in recent trials.

Methods: Randomised superiority trials of first-line chemotherapy or targeted therapy for HER2-negative mBC including >150 patients, meeting the primary efficacy objective and published between 2000 and 2014 were identified. The sample sizes required to power for PFS (or TTP) and OS were calculated retrospectively for each trial using the observed results and study/recruitment follow-up durations (alpha=0.05, 2-sided log-rank test, 80% power), and summarised as a factor relative to the actual sample size ($x < 1$ required x-fold fewer cases to show the same gain; $x > 1$ required x-fold more cases).

Results: Only 8 of the 14 identified trials reported all information required for retrospective sample size calculation (Table). Most would have required a far larger sample size to demonstrate an OS gain (x: 0.5–2479) with the observed results. In 10 of 13 trials, the sample size required to power for OS was at least 5-fold larger than that needed to power for PFS.

Conclusions: Designing trials to test potential new treatments for HER2-negative mBC is challenging and requires a balance of regulatory acceptability, feasibility and realistic medical assumptions to calculate sample sizes, which can be particularly difficult in heterogeneous study populations with long post-progression survival and heterogeneous subsequent therapies. However, ongoing and future trials of cancer immunotherapy (new mode of action) focusing on triple-negative mBC (a more homogeneous population with shorter OS and post-progression survival, and fewer treatment options) may show a new pattern.

Legal entity responsible for the study: Roche Pharma AG

Funding: Roche Pharma AG

Disclosure: S. Kümmel, C. Jackisch: Membership on advisory board: Roche Pharma AG. V. Müller: Membership on advisory board or board of directors: Amgen,

Table: 267P Summary of results

Study	Total No. of patients in trial (randomisation if not 1:1)	Observed median, months (arm A v B)			Retrospectively calculated sample size		Factor (x)	
		PFS	TTP	OS	PFS/TTP	OS	OS sample size/N	OS/PFS sample size
Ackland 2001	460[a]	–	6.3 v 8.7[b]	18.2 v 20.1	360	5906	12.8	16.4
Jassem 2001	267[a]	–	6.2 v 8.3[b]	18.3 v 23.3[b]	592	1792	6.7	3.0
Ejlertsen 2004	387[a]	8.2 v 10.1[b]	–	18.0 v 19.1	788	11 988	31.0	15.2
Bontenbal 2005	216	–	6.6 v 8.0[b]	16.2 v 22.6[b]	1022	476	2.2	0.5
Feher 2005	397[a]	–	3.4 v 6.1[b]	11.8 v 19.1[b]	98	212	0.5	2.2
von Minckwitz 2005	364[a]	–	6.7 v 8.2[b]	–	820	–	–	–
Paridaens 2005	331[a]	3.9 v 7.5[b]	–	15.6 v 18.3	80	1882	5.7	23.5
Albain 2008	529	–	4.0 v 6.1[b]	15.8 v 18.6[b]	168	1404	2.7	8.4
Gray 2009	722	5.8 v 11.3[b]	–	24.8 v 26.5	72	8262	11.4	114.8
Sparano 2009	751	–	7 v 9.8[b]	20.6 v 20.5	294	1 862 010	2479.4	6333.4
Miles 2010	488 (1:1:1)	8.2 v 10.1[b]	–	31.9 v 30.2	802	20 802	42.6	25.9
Robert 2011	615 (1:2)	5.7 v 8.6[b]	–	22.8 v 25.7	234	3840	6.2	16.4
Gligorov 2014	185	4.3 v 11.9[b]	–	23.7 v 39.0[b]	34	242	1.3	7.1
Lorusso 2014	233	–	7.8 v 9.4[b]	28.0 v 30.1	972	9654	41.4	9.9

[a]Duration of accrual and/or follow-up not reported; accrual period assumed to be 1/3 of study duration.
[b]Statistically significant.

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268P What are the treatment patterns and overall survival (OS) in patients with metastatic triple-negative breast cancer (mTNBC) in US clinical practice?

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Background: mTNBC is a condition with significant unmet medical need due to limited treatment (tx) options and short survival after chemotherapy (chemo) failure. Tx patterns and OS in patients (pts) with mTNBC in US clinical practice were assessed.

Methods: This retrospective chart review study used data collected in October and November 2016 from US oncologists via an online case report form. Data of adult pts who were initiated on a pharmacological tx after a diagnosis of recurrent or de novo mTNBC between January 2012 and June 2015 were reviewed. Tx regimens used in 1st- and 2nd-lines for mTNBC were summarized. Median OS from 1st- and 2nd-line tx initiation were estimated using Kaplan-Meier analyses.

Results: 125 oncologists provided data on 411 mTNBC pts; mean age was 57 years; 298 (73%) had ≥2 lines of tx; 256 different tx sequences were identified. Mean duration of tx was 7.5 months (mos) in 1st-line and 7.3 mos in 2nd-line. The most prevalent tx regimens were single agent chemo with taxane (22%) in 1st-line and capecitabine (Cap; 20%) in 2nd-line. Median OS was 16.7 mos in 1st-line and 14.2 mos in 2nd-line.

Conclusions: Findings suggest that, in US clinical practice, there is substantial heterogeneity in the tx of pts with mTNBC. Pts had a median OS < 18 mos after tx initiation. A better understanding of the mTNBC pt subpopulation and optimal tx sequencing is warranted to improve tx strategies and prolong survival.

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Table: 268P

1st-line, N = 411	%	**Median OS [95% CI], mos**
All	-	**16.7 [15.2; 18.0]**
Single agent	45	15.6 [13.2; 18.6]
Combination	55	17.0 [15.1; 19.1]
Tx regimen		
Single agent taxane (docetaxel/paclitaxel (pac)/nab-pac)	22	–
Anthracycline (ATC; doxorubicin [Dox]/epirubicin/liposomal Dox) + cyclophosphamide +/- taxane	14	–
Platinum (carboplatin/cisplatin/oxaliplatin) + taxane	13	–
Bevacizumab-containing	10	–
Gemcitabine (Gem) + platinum	10	–
Cap	9	–
Other	21	–
2nd-line, N = 298		
All	-	**14.2 [10.5; 22.3]**
Single agent	72	12.9 [10.5; 22.3]
Combination	28	16.2 [8.1; -]
Tx regimen		
Cap	20	–
Platinum-containing (w/o taxane)	13	–
Single agent taxane	13	–
Taxane-containing combination	12	–
Eribulin	9	–
ATC-containing (w/o taxane or platinum)	8	–
Gem	7	–
Other	16	–

269P Outcomes of systemic therapy for advanced triple-negative breast cancer: A single centre experience

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Background: Systemic treatment outcomes for advanced triple-negative breast cancer (aTNBC) are worse compared to other disease subtypes, due to aggressive behaviour, heterogeneity and lack of molecular targets. Many options are under investigation although most patients receive standard cytotoxic chemotherapy. We aimed to provide better insight into the efficacy of different lines of therapy for aTNBC (overall response rate [ORR], median progression-free survival [mPFS] and median overall survival [mOS]) to better inform discussion with patients, decision-making and referral for clinical trials.

Methods: We retrospectively identified 268 patients diagnosed with aTNBC from 01/12/2011 to 30/11/2016 from our electronic records. Patients' and tumour characteristics were recorded, along with systemic treatment outcomes. Chi-squared/Fishers exact test and Kaplan-Meier statistical methods were utilised.

Results: 186 patients treated with ≥1 line of palliative systemic treatment were eligible for the analysis with a median age at 55 (range 26-91). 53.8% had ECOG Performance Status 0 and 69.9% visceral involvement. 38.6% had a disease-free interval (DFI) <12 months following surgery and 13.4% had de novo advanced disease. 11.4% carried a BRCA mutation. 64.5% received 2 lines of therapy, 37.6% had 3 and 21.5% had 4. ORR and mPFS to first line therapy were respectively 43.9% (95% CI 36.5-51.5) and 3.7 months (95% CI 2.9-5.1), to second line was 40.2% (95% CI 31.2-49.6) and 3.5 months (95% CI 2.6-4.1), to third line 28.8% (95% CI 18.3-41.3) and 2.5 months (95% CI 2.0-3.0) and to fourth line 25.0% (95% CI 12.7-41.2) and 2.1 months (95% CI 1.6-2.8). First line patients with a DFI ≥12 months had ORR of 47.7% (95% CI 36.8-58.7) compared to 35.8% (95% CI 23.1-50.2) for those with a DFI <12 months (p 0.172). mPFS was respectively 5.2 months (95% CI 3.4-6.5) compared to 2.7 (95% CI 1.8-3.6) (p 0.005).

Table: 269P Demographics at advanced stage disease diagnosis

Median age	55 (range: 26-91)	
Age group N (%)	**< 60 years**	117 (62.9)
	≥ 60 years	69 (37.1)
ECOG Performance Status N (%)	**0**	100 (53.8)
	1	75 (40.3)
	2	11 (5.9)
Disease sites N (%)	**Visceral**[1]	130 (69.9)
	Non-visceral only	56 (30.1)
Advanced disease histology N (%)	**Invasive ductal**	112 (60.2)
	Invasive lobular	7 (3.8)
	Mixed	2 (1.1)
	Metaplastic	3 (1.6)
	Other	2 (1.1)
	Not available[2]	60 (32.3)
De novo advanced disease N (%)	25 (13.4%)	
No. of lines of systemic therapy received N (%)	**1**	186 (100)
	2	120 (64.5)
	3	70 (37.6)
	4	40 (21.5)
	5	20 (10.7)
	6	5 (2.7)
	7	1 (0.5)
DFI[3]	**≤12 months**	56 (38.6)
	>12 months	89 (61.4)
BRCA	**Wild-type**	66 (35.7)
	Mutated[4]	21 (11.4)
	Unknown	98 (53.0)

[1]: with or without non-visceral involvement; [2]: radiological diagnosis of advanced disease; [3]: 145 (80%) patients included in the DFI analysis; [4]: either BRCA1 or BRCA2.

Conclusions: The response rates observed in this population of patients are similar to those observed in published clinical trials. However, the PFS rates are short, and as a result early consideration for inclusion in clinical trials of novel approaches can be justified in these patients.

Legal entity responsible for the study: Nicolò Matteo, Luca Battisti

Funding: None

Disclosure: All authors have declared no conflicts of interest.

270P Untreated hormone receptor positive/HER2-negative metastatic breast cancer survival with front-line chemotherapy and maintenance endocrine therapy

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Background: Except some life threatening cases, combination of endocrine therapy and CDK4/6 inhibitors is becoming the standard first line treatment for women with hormone receptor (HR) positive/HER2 negative advanced and metastatic breast cancer (MBC). However cost-effectiveness analyzes are lacking concerning this therapy. As chemotherapy also targets cell cycle we wondered how sequential combination of chemotherapy and maintenance endocrine therapy could be effective as first line treatment for naive HR+/Her2- MBC.

Methods: We retrospectively collected from our institutional database ("Institut Paoli-Calmette", Marseille, France) cases with naive HR+/HER2- MBC. We selected patients treated with chemotherapy plus maintenance endocrine therapy as first line treatment between January 2000 and December 2015. Progression-free survival (PFS) and Overall Survival (OS) were analyzed using the Kaplan-Meier's method. We also conducted univariate (UV) and multivariate analyzes including menopausal status, visceral disease, pathological subtype, and progesterone receptor expression assessed by immunohistochemistry.

Results: A total of 183 female patients were included with a median age at diagnostic of 56,9 years. Most of them were postmenopausal (n = 114, 65.9%) and 108 (59.7%) had visceral metastases. Anthracyclynes-Taxanes combinations were used for 162 patients (88.5%). Median number of chemotherapy cycles was 6. Endocrine therapy was aromatase inhibitors and tamoxifen for 120 (67.8%) and 56 (31.6%) cases, respectively. Median PFS was 33 months [95CI = 25-38] and median OS was 79 months [95CI = 63-101]. In UV analysis pre-menopausal status (HR = 0.58), non-ductal non-lobular subtype (HR = 0.47), and absence of visceral disease (HR = 0.51) were correlated to better OS. All these features remained significant in multivariate analysis. We observed no death related to treatment.

Conclusions: Following these results, and with the issues of cost-effectiveness related to newly approved therapies, first-line chemotherapy plus maintenance endocrine therapy may be considered for untreated HR+/HER2- MBC.

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271P Can we predict subsequent brain metastasis in patients with metastatic breast cancer?

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Background: The one year over all survival of breast cancer patients with brain metastasis is only 20%–40%. Approximately, 80% of brain metastases occur after the diagnosis of other systemic metastatic lesions. Due to this dismal prognosis, prophylactic approaches as cranial irradiation, high-dose methotrexate, or lapatinib could be evaluated as preventative measures. However, these approaches are usually toxic and cannot be applied to all patients. This study is carried out to evaluate risk factors that have an impact on subsequent development of brain metastasis in metastatic breast cancer patients and thus, those patients can be candidates for prophylactic measures.

Methods: The medical files of 267 metastatic patients were retrospectively reviewed for demographic, clinico pathological, metastatic and treatment characteristics.

Results: 46 out of 267 patients developed brain metastasis with an incidence of 17.2%. Significant risks include age <40y 28.7% patients compared to21.6% for age 40 – 50y and 11.1% for age >50y (P = 0.031), 24.2% premenopausal patients compared to 11.4% for postmenopausal (P = 0.013), Her2/neu overexpression (48.5%) and triple negative (35.3%) compared to 11.3% patients with ER positive (P = 0.0001, 0.003), high grade compared to low grade tumors (35.6% vs 12.6% P = 0.005). Patients with N2, 3 had higher risk than N0, 1 (44% vs 13.8%) (P = 0.01), 30.9% patients with disease free duration (DFD) <2 years developed brain metastasis compared to 22.1% for M1 patients and 11.1% patients with DFD >2years (P = 0.019, 0.033). 3.6% patients with bone only metastasis developed brain metastasis compared to 20.6% patients with visceral only metastasis and 27.4% patients with bone and visceral metastasis (P = 0.036, 0.014). 32.3% patients with lung containing metastasis developed brain metastasis

compared to 57.3% patients with lung and liver containing metastasis and 9.2% of patients with liver containing metastasis (P = 0.038, 0.022).

Conclusions: Young patients with lung metastases, Her2/neu overexpression or triple negative with disease free duration < 2years carried the highest risk for brain metastases. Such patients may be candidate for screening or prophylactic strategies.

Legal entity responsible for the study: Ethics committee, Faculty of Medicine, Alexandria University.

Funding: None

Disclosure: All authors have declared no conflicts of interest.

272P Pathological characteristics and prognosis of a cohort of 57 patients (pts) with de novo oligometastatic breast cancer (OMBC)

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Background: Management of de novo OMBC is controversial with no specific treatment guidelines available.

Methods: We reviewed 57 consecutive de novo OMBC pts defined as ≤ 5 synchronous metastatic lesions, diagnosed between 01/2000 and 12/2012 at Oscar Lambret Center. Clinicopathological (CP) characteristics and survival data were retrospectively collected. Predictors of overall survival (OS) and progression free survival (PFS) were identified by univariate analysis before being introduced into a stepwise cox regression model.

Results: Median primary tumor size was 40mm (0-150) and 79% of the cases were invasive ductal carcinoma. Estrogen and progesterone receptors were detected in respectively 76% and 56% of the cases. HER2 overexpression was observed in 26% and 12.5% were triple negative. Median KI67 was 40% (5-80). On SBR grading, 3 (6%) cases were grade I, 31 (66%) grade II and 12 (26%) grade III. 16% pts had ≥ 4 histologically involved axillary lymph nodes. The median number of metastatic lesions was 2 (1-5). 31 pts had bone metastases. 65% pts were treated surgically for the primary tumor, 42% had neoadjuvant (NA)/adjuvant chemotherapy (CT), 45% had radiotherapy (RT) for primary BC and 58% were locally treated for their metastatic lesions, while 17 pts were treated with palliative CT only. The median follow-up period was 6.4 years (0.2–12). 2 and 5-year OS and PFS were respectively 90.8%/52.1% and 45.7%/21.4%. Significant predictors of both OS/PFS in univariate analysis were SBR grade, surgery and RT of primary BC, use of NACT and hormonotherapy. In multivariate analysis (MV) both SBR ≤ 2 at diagnosis and the administration of NA CT were identified as significant predictors for better OS (p = 0.005 and 0.006 respectively). High SBR grade independently predicted for worse PFS (p = 0.006).

Conclusions: This retrospective work further highlights the CP characteristics and predictors of outcome of de novo OMBC pts. Only SBR grade at diagnosis and use of NA CT were identified as significant predictors in MV analysis. A molecular analysis of this cohort is planned to complete these findings and characterize the subset of OMBC pts who could benefit from curative therapy and those for whom alternative strategies should be adopted.

Legal entity responsible for the study: Centre Oscar Lambret

Funding: None

Disclosure: All authors have declared no conflicts of interest.

273P External validation of modified breast graded prognostic assessment for breast cancer patients with brain metastases

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Background: Several prognostic indexes have been developed to estimate survival of breast cancer (BC) patients with brain metastases (BM). The Modified Breast Graded Prognostic Assessment (GPA) has been proposed as refinement of the Breast GPA, based on a single-institution cohort of 1,552 patients. In addition to age, tumor subtype and Karnofsky PS, the modified breast GPA comprises number of BM. The aim of this study is to validate the modified breast-GPA in an external multinational cohort.

Methods: Clinical and biological data of 668 BC patients diagnosed with BM at four European institutions between 1996 and 2016 were reviewed. Patients were classified according to breast GPA and modified breast GPA. OS was calculated from time of BM diagnosis to death or last follow up. Cox proportional models were used to calculate Hazard Ratio and 95% Confidence Intervals (CI). Performances of breast-GPA and modified breast-GPA were compared using Harrell's concordance index.

Results: At last follow-up, 632 patients (94.6%) had died. Median OS was 8.1 months (95% CI 6.9-9.4 months). Median age at BM diagnosis was 56 years (range 24-85). Tumor phenotype distribution was: triple negative (20.1%), hormone receptor (HR)-HER2 + (21.6%), HR+HER2 + (20.4%) and HR+HER2- (33.4%). KPS distribution was: 90-100 (19.6%), 70-80 (49.0%), 60 (12.8%) and ≤50 (18.6%). 355 patients (53.5%) had >3 BM. Number of BM (1,2,3,>3) was significantly associated with OS (p < 0.001). Both breast-GPA and modified breast-GPA predicted OS (Table). Concordance indices were 0.641 (95% CI, 0.6405 to 0.6422) and 0.667 (95% CI, 0.6662 to 0.6678) for breast-GPA and modified breast-GPA, respectively (p < 0.001).

Conclusions: Number of BM is a significant prognostic factor in BC patients with BM and modified breast-GPA performs better than breast-GPA in predicting prognosis of these patients.

Legal entity responsible for the study: Department of Surgery, Oncology and Gastroenterology, University of Padova, Padua, Italy

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Disclosure: All authors have declared no conflicts of interest.

Table: 273P

Breast GPA category	Number of patients (%)	Median OS, months (95% CI)	Hazard Ratio (95% CI)	p
3.5-4	86 (13.5%)	18.8 (14.5-22.6)	ref	<0.001
2.5-3	248 (38.8%)	10.3 (8.8-11.8)	1.45 (1.12-1.88)	
1.5-2	194 (30.4%)	6.2 (4.9-7.6)	2.04 (1.56-2.66)	
0-1.0	111 (17.4%)	2.5 (1.8-3.2)	4.97 (3.67-6.71)	
Modified breast GPA category	Number of patients (%)	Median OS, months (95% CI)	Hazard Ratio (95% CI)	p
3.5-4	37 (5.8%)	18.9 (17.2-20.5)	ref	<0.001
2.5-3	209 (32.8%)	15.2 (12.1-18.3)	1.43 (0.98-2.09)	
1.5-2	257 (40.3%)	7.9 (5.9-9.9)	2.30 (1.59-3.33)	
0-1.0	135 (21.2%)	2.3 (1.9-2.8)	7.03 (4.72-10.46)	

274P Baseline characteristics and first-line (1L) treatment of patients with HER2+ metastatic breast cancer (MBC) from the SystHERs registry

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Background: The addition of pertuzumab (P) to trastuzumab (H) and docetaxel improves survival in clinical trials of patients with HER2+ MBC, and is a guideline-recommended standard of care for this population. In the real world, however, various factors may influence treatment decisions. Systematic Therapies for HER2-positive Metastatic Breast Cancer Study (SystHERs) is a fully enrolled (June 2012–June 2016), ongoing, US-based, observational study that captures real-world data for patients with HER2+ MBC. Here, we describe the baseline characteristics and treatment patterns of patients who received 1L PH or H without P.

Methods: Eligible patients had HER2+ MBC diagnosed within 6 months of enrollment and were ≥18 years of age. Patients were compared descriptively by 1L treatment (PH vs H without P), defined as any therapy received up to first progression.

Results: As of February 10, 2017, among 978 eligible patients, 949 had received 1L treatment (PH, n = 711; H without P, n = 174; no H, n = 64) (Table). 476 (67%) and 88 (51%) of patients in the 1L PH and H without P cohorts, respectively, remain on study. Median follow-up from 1L treatment start was 22 and 25 months, respectively. In patients treated with PH, median duration of treatment with H and P were 15 and 13 months, respectively. In the H without P cohort, median duration of H was 15 months. Among all patients, 68% (648/949) received 1L PH + taxane.

Conclusions: Of patients with HER2+ MBC in the real-world SystHERs study, 68% were treated with PH + taxane. Compared with patients who received PH, those who received H without P were older, less commonly had liver metastasis, and more commonly had prior cardiovascular disease, suggesting that these characteristics may have influenced the treatment choice between PH vs H without P.

Clinical trial identification: NCT01615068

Legal entity responsible for the study: Genentech/Roche

Funding: Genentech/Roche

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275P First-line treatment patterns by age for patients (pts) with HER2+ metastatic breast cancer (MBC) in the SystHERs registry

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Background: Clinical outcomes for pts with HER2+ MBC may differ by age, potentially influenced by differences in treatment regimens administered to older vs younger pts. Systematic Therapies for HER2+ Metastatic Breast Cancer Study (SystHERs) captures real-world treatment patterns and outcomes in pts with HER2+ MBC. Here, we

Table: 274P

	PH (n = 711)	H without P (n = 174)
Baseline characteristics		
Median age at MBC diagnosis, years (range)	55 (21–89)	61 (28–90)
White, n (%)	565 (79)	137 (79)
Eastern Cooperative Oncology Group performance score 0–1, n (%)	613 (86)	146 (84)
Private insurance, n (%)	367 (52)	83 (48)
Urban or suburban living location, n (%)	556 (78)	138 (79)
De novo, n (%)	379 (53)	88 (51)
Estrogen receptor positive and/or progesterone receptor positive, n (%)	496 (70)	126 (72)
Visceral, n (%)	476 (67)	108 (62)
≥3 metastatic sites, n (%)	232 (33)	43 (25)
Liver metastasis, n (%)	300 (42)	47 (27)
Central nervous system (CNS) metastasis, n (%)	45 (6)[a]	15 (9)[a]
Prior cardiovascular disease, n (%)	80 (11)	31 (18)
Treatment for early breast cancer[b], n (%) Any neoadjuvant or adjuvant therapy Any H	n = 332 293 (88) 187 (56)	n = 86 72 (84) 46 (53)
1L treatment patterns, n (%) (Treatments are not mutually exclusive)		
With chemotherapy Taxane Docetaxel Paclitaxel Platinum	673 (95) 648 (91) 479 (67) 195 (27) 69 (10)	117 (67) 87 (50) 34 (20) 51 (29) 40 (23)
With hormonal therapy Aromatase inhibitor Tamoxifen	282 (40) 221 (31) 61 (9)	94 (54) 76 (44) 14 (8)

[a] In patients who did not receive H, 25% (16/64) had CNS metastasis.
[b] In patients with recurrent disease.

Table: 275P

	<50 years (n = 287)	50-69 years (n = 563)	≥70 years (n = 128)
Baseline characteristics			
Median age at MBC diagnosis, years (range)	43 (21–49)	59 (50–69)	75 (70–90)
Eastern Cooperative Oncology Group performance score 0–1, n (%)	249 (87)	476 (85)	101 (79)
De novo, n (%)	158 (55)	278 (49)	52 (41)
Median time from early breast cancer diagnosis to MBC diagnosis[a], months (range)	36 (9–166)	50 (5–329)	42 (4–452)
Estrogen receptor positive and/or progesterone receptor positive, n (%)	203 (71)	387 (69)	96 (75)
Visceral disease, n (%)	196 (68)	378 (67)	75 (59)
≥3 metastatic sites, n (%)	87 (30)	183 (33)	32 (25)
Bone metastasis, n (%)	165 (57)	282 (50)	57 (45)
Liver metastasis, n (%)	117 (41)	216 (38)	33 (26)
First-line treatments, n (%) (Treatments are not mutually exclusive)			
Any HER2-targeted therapy PH H without P	275 (96) 229 (80) 37 (13)	531 (94) 414 (74) 93 (17)	116 (91) 68 (53) 44 (34)
Any chemotherapy PH + taxane H without P + taxane	254 (89) 207 (72) 18 (6)	489 (87) 386 (69) 53 (9)	86 (67) 55 (43) 16 (13)
Any hormonal therapy With PH With H without P	113 (39) 91 (32) 18 (6)	230 (41) 161 (29) 48 (9)	67 (52) 30 (23) 28 (22)
Breast cancer -specific survival, % (95% confidence interval)			
Breast cancer–specific survival rate 12 months 24 months 36 months	95 (92–97) 86 (81–90) 78 (71–84)	92 (89–94) 80 (76–84) 68 (63–73)	92 (85–95) 80 (71–87) 64 (48–76)

[a]In pts with recurrent MBC only. H, trastuzumab; P, pertuzumab.

examine baseline characteristics, first-line treatments, and breast cancer–specific survival (BCSS) by age.

Methods: SystHERs is a fully enrolled (Jun 2012–Jun 2016), ongoing, US-based, observational study. Pts were ≥18 years old and had HER2+ MBC diagnosed within 6 months of enrollment. Pts were grouped by age at MBC diagnosis (<50, 50–69, or ≥ 70 years) and compared descriptively. BCSS was defined as time from the date of MBC diagnosis to date of death due to MBC progression.

Results: As of Feb 10, 2017, of 978 eligible pts, 287 were <50 years old, 563 were 50–69, and 128 were ≥70 at MBC diagnosis. Median follow-up from MBC diagnosis was 23, 22, and 19 months, respectively. Baseline characteristics, first-line treatments, and BCSS are shown (Table). In pts who received chemotherapy, docetaxel was the most common agent in pts <50 (67%) and 50–69 (64%) followed by paclitaxel (29% in both groups), whereas in pts ≥70, 43% and 45% received docetaxel and paclitaxel, respectively.

Conclusions: In this preliminary real-world analysis of pts with HER2+ MBC, pertuzumab (P) + trastuzumab (H) was more commonly used than H without P across all age groups. Pts <50 and 50–69 years old more commonly received PH + taxane than those ≥70 (72% and 69% vs 43%, respectively). Compared with younger pts, those ≥70 received regimens with chemotherapy less commonly (89% and 87% vs 67%), and more commonly received regimens with H without P (13% and 17% vs 34%) or hormonal therapy (39% and 41% vs 52%). Pts <50 had longer BCSS than those ≥70 (78% vs 64% at 3 years).

Clinical trial identification: NCT01615068

Legal entity responsible for the study: Genentech/Roche

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276P Defining priorities for research: Interim results of the Canadian metastatic breast cancer priority setting partnership

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Background: Research priorities are generally determined by funders and researchers without direct involvement and input from patients and caregivers. Certain disease areas have incorporated the patient voice to determine patient driven priorities. In this study, this approach was employed to better understand the needs and priorities of metastatic breast cancer patients and their caregivers.

Methods: This study was conducted using methodology outlined by the James Lind Alliance. A steering committee of patients, physicians, patient advocates, and allied health care professionals was assembled to oversee the research study. The initial survey collected unanswered research questions from patients, caregivers, and clinicians. Responses were collected and categorized by consensus of the steering committee. Here we present the results from the national survey.

Results: Between November 2016 and April 2017, 733 responses from 311 individuals were collected (62% patients, 11% physicians, 9% caregivers or relatives, 5% nurses/allied health professionals, 2% patient organization representatives, and 10% other). The main themes for key patient priorities are: 136 (19%) related to treatment and monitoring, 78 (11%) linked lifestyle and alternative therapy, 58 (8%) regarded tumour biology, 53 (7%) regarded psychosocial aspects, 46 (6%) to diagnosis, 35 (5%) to toxicity, 24 (3%) to prevention, and 17 (2%) to young or pre-menopausal population. Two hundred and eighty-six (39%) were considered out of scope. The most frequently identified priorities included the role of alternative therapies for improving survival, the role of immune therapy for treating metastatic breast cancer, and the potential for improving outcomes with early detection/surveillance with modern treatment and diagnostic modalities.

Conclusions: Patient derived research priorities in advanced breast cancer point to an improved understanding of alternative therapies, integration of immune therapy and a focus on early detection of relapse. These priorities should be addressed by the research community to meet the needs of our patients with advanced breast cancer.

Legal entity responsible for the study: Nancy Nixon

Funding: None

Disclosure: S. Verma: Advisory Boards for: Roche, Pfizer, Novartis, Eli Lilly, Merck, Amgen. All other authors have declared no conflicts of interest.

277P Real-world treatment patterns and outcomes among elderly metastatic triple negative breast cancer patients in the United States

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Background: Triple negative breast cancer (TNBC) is more aggressive than other breast cancer (BC) subtypes and accounts for up to 20% of all BC. Despite the poorer prognosis, there are no approved targeted treatments available and chemotherapy (chemo) remains the only choice. We examined treatment patterns and outcomes among elderly metastatic TNBC patients (pts) in routine clinical practice.

Methods: Patients were identified from the linked SEER-Medicare database (1/1/2001-12/31/2013). The analysis included TNBC *de novo* Stage IV pts (n = 776) and pts with distant recurrences following an initial diagnosis of Stage I-III (n = 1851). Pts were ≥66 years and continuously enrolled in Medicare Parts A/B in the year prior to diagnosis. The analysis was stratified by age <70 (n = 359) and ≥70 (n = 2268). Kaplan Meier analyses and time-varying Cox proportional hazards regression assessed overall survival (OS).

Results: The mean age at metastatic diagnosis was 77.6 years and 1259 (48%) pts received treatment with chemo. Compared to < 70 year olds, ≥70 year olds were less likely to be diagnosed with *de novo* Stage IV disease (28% vs. 42%), had worse performance status indicators, higher comorbidity burden, were less likely to receive chemo (45% vs. 66%), but were more likely to have had BC surgery (81% vs. 70%). Pts treated with chemo had improved OS compared to untreated pts, and the survival advantage was more pronounced in the <70 year olds with a 6 month longer unadjusted OS compared to the ≥70 cohort (log rank p < 0.0001). This finding was supported in the adjusted multivariate model which showed a 46% (HR = 1.46; 95% CI: 1.08-1.96) increased risk of death for untreated pts in the <70 year olds and a 17% (HR = 1.17; 95% CI: 1.06-1.29) increased risk of death for untreated pts in the ≥70 year olds (vs. treated).

Conclusions: In this real-world analysis, 52% of elderly TNBC pts did not receive chemo following their metastatic diagnosis. Although the survival benefits of chemo were stronger in the younger cohort, the benefits of treatment were maintained among ≥70 year olds who were also less likely to receive chemo. These findings suggest opportunities exist to improve the clinical treatment of elderly TNBC pts.

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278P Effect of neoadjuvant chemotherapy on disease free survival and over all survival in triple-negative breast cancer patients

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Background: Breast cancer (BC) is the most common cancer in India with 150000 new cases are diagnosed and 70000 women dies of it every year. Triple-negative breast cancer (TNBC) is an aggressive subtype that lack ER and PR expression and absence of overexpressed or amplified HER2. TNBC accounts for 15%-25% of all invasive BC, occurs more in younger women and is associated with higher histologic grade and advanced disease. Our goal was to study the relation between triple-negative receptor status and major determinants of clinical outcome, such as response to neoadjuvant chemotherapy (rate of pathologic complete response [pCR]), progression free survival (PFS), site-specific distribution of recurrence, postrecurrence survival (PRS) and overall survival (OS).

Methods: We included 2658 patients who received neoadjuvant chemotherapy at Jawaharlal Nehru Cancer Hospital Bhopal for stage I-III breast cancer from 1990 to 2010 and for whom complete receptor information were available. Clinical and pathologic parameters, pCR, survival measurements and organ-specific relapse rates were compared between patients with TNBC and non-TNBC.

Results: 505 patients (19%) had TNBC. Mean age for TNBC (42 years) was lesser than non-TNBC (56 years; *P*=.002). Patients with TNBC had significantly higher pCR rates (34% *v* 14%; *P*=.028) but decreased 5 year PFS rates (*P*<.0001) and 5year OS rates (*P* <.0001). TNBC was associated with increased risk for distant metastases (*P* =.0005), lower risk for bone recurrence (*P* = .034) and shorter PRS (*P* < .0001). Recurrence and death rates were higher for TNBC only in the first 5 years. If pCR was achieved, patients with TNBC and non-TNBC had similar survival (*P* = .36). Patients with residual disease (RD) had worse OS if they had TNBC compared with non-TNBC (*P* < .0001).

Conclusions: TNBC patients have increased pCR rates (excellent survival) compared with non-TNBC. However TNBC patients with RD have significantly worse survival after neoadjuvant chemotherapy in first 5 years.TNBC patients may be best treated with 3rd generation adjuvant or neoadjuvant chemotherapy regimens that achieve the highest possible pCR rates. With high risk of distant metastases, these patients require closer surveillance in initial years of follow-up.

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Legal entity responsible for the study: Jawaharlal Nehru Cancer Hospital, Bhopal, India

Funding: None

Disclosure: All authors have declared no conflicts of interest.

279P Real-world everolimus experience in postmenopausal HR+ HER2- advanced breast cancer women: Treat ER+ight Canadian prospective observational study 2nd subgroup analysis

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Background: Treat ER^{+}ight is the 1st Canadian real-world study enrolling patients (pts) previously exposed to letrozole or anastrozole and currently receiving endocrine therapy (ET) alone or in combination with targeted therapy.

Methods: At data cut-off (13 Mar '17), 35 pts were enrolled in the everolimus + exemestane (EVE+EXE) subgroup out of 100 total enrolled pts since Mar '16 from 24 active sites. This sub-analysis describes baseline characteristics, treatment duration and stomatitis prevention outcomes in EVE+EXE pts.

Results: Baseline characteristics: median age – 65 (39-80); family history of breast cancer (BC) – 37%; ECOG 0-1 – 83%; median time since primary BC diagnosis – 6 yrs (2-12); median time since advanced BC diagnosis – 1 yr (0-3.5). Sites of metastases (%): bone (B) only – 26; visceral (V) only – 43; B+V – 23. Line (L) of metastatic therapy (%): 17 - 1L, 51 - 2L, 31 - 3L. EVE start dose (%): 10mg (80), 7.5mg (3), 5mg (17). Therapy ongoing n (%): 23 (66) (78% 1L & 2L). Therapy discontinued n (%): 12 (34) (50% 3L). Reason for discontinuation n (%): 9 (75) progression, 2 (17) adverse event, 1 (8) death. Median follow-up time at data cut-off 3.4 mths (0.5-9.1). Median time to treatment discontinuation (TTD) 7.0 mths (95% CI, 3.4-NR) in overall subgroup. Median TTD NR (95% CI, 2.4-NR) in 20 (57%) pts receiving prophylactic/proactive mouthwash (P/P MW) compared to 5.7 mths (95% CI, 3.2-NR) in 15 (43%) pts receiving reactive/no MW (p = 0.140, Log-rank). 1st stomatitis event related to EVE n (%): overall subgroup 10 (29) – any Grade (Gr), 7 (20) – Gr 1, 2 (6) – Gr 2, 1 (3) – Gr 3 and in P/P MW subgroup 3 (15) – any Gr. Median time to 1st stomatitis event in P/P MW subgroup (mths) NR (95% CI, 1.64-NR) and NR (95% CI, 0.33-NR) in reactive/no MW subgroup (p = 0.334, Log-rank) with majority of stomatitis events occurring early within the 1st 2 months of therapy.

Conclusions: Compared to BOLERO-2, EVE+EXE pts in Treat ER+ight had lower ECOG 0-1 (83 vs 96%), more V disease (66 vs 56%), 20% received lower EVE start dose, similar treatment duration (7.0 mths median TTD vs 7.8 mths median PFS) and lower any Gr stomatitis (29 vs 59%). This represents the 1st observation of a trend toward improved TTD in pts receiving P/P MW upon EVE initiation.

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Legal entity responsible for the study: Novartis Pharmaceuticals Canada Inc.

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280P FICHE-YOUNG: FIrst-line treatment CHoicE in hormone receptor positive (HR+)/HER2- negative metastatic breast cancer patients (MBC) ≤45 years old. A large observational multicenter cohort survival analysis

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Background: Metastatic breast cancer (MBC) in young patients (pts) is traditionally considered at poor prognosis. Although current guidelines recommend endocrine therapy (ET) as first line treatment (1st trt) for HR+ HER2- MBC, younger age can lead to more extensive use of first line chemotherapy (CT). In the present analysis, we aimed to

assess overall survival (OS) of younger MBC pts compared to older ones, and to explore 1st trt choices in a large real-life multicenter cohort.

Methods: The Epidemiological Strategy and Medical Economics (ESME) Research program aims to collect high-quality real-world data in oncology from 18 French Comprehensive Cancer Centers. Pts who started treatment for a newly diagnosed MBC between Jan 2008 and Dec 2014 were selected in the MBC ESME database. The primary end point of the FICHE-Young study was to compare adjusted OS in pts diagnosed with endocrine-sensitive HR+ HER2- MBC and aged ≤45 vs > 45 at diagnosis. We also evaluated 1st trt choices in both categories and its correlation with OS. Analyses will be adjusted on a propensity score, in order to control selection biases associated with non-randomization.

Results: 6265 pts out of 16703 in ESME had HR+/HER2- MBC. Characteristics and 1st trt choices are listed in the Table. Median OS was 62.3 months (mos) (95% CI 56.5-69) in pts ≤45 and 52.8 mos in those >45 (95% CI 50.7-55), p<.0001. In pts ≤45, we did not show any statistically significant difference in OS between first line ET and CT+/-ET (68.5 mos for ET (95% CI, 56.8-NE) vs 59.0 mos for CT+/-ET (95% CI, 55.9-69), p = 0.3208).

Table: 280P

	≤ 45 yrs old	>45 yrs old
N	851	5414
Median age	40.0 [23;44]	63 [45;95]
Visceral metastases	56.3%	51.6%
De novo MBC	41%	42.4%
Median time to onset of MBC	3.28 yrs [0.50;19.53]	9.18 yrs [0.50;43.02]
1st trt: ET alone	19.4%	47.4%
Chemo +/- maintenance ET	80.6%	52.6%

Conclusions: With the limitations of a nonrandomized study population, in this real-world setting, younger HR+MBC pts did not show a poorer prognosis compared to older patients. Many young pts received CT as first line treatment, with no demonstrated benefit over ET alone.

Legal entity responsible for the study: UNICANCER

Funding: UNICANCER

Disclosure: All authors have declared no conflicts of interest.

281P Cell-free circulating DNA as independent prognostic markers in metastatic breast cancer

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Background: Blood-based biomarkers like microRNAs, cell-free DNA and circulating tumor cells hold great promise as they are reproducible and easily accessible in cancer patients. Cell-free DNA variables, such as cell-free DNA concentrations (cfDNA conc) and cell-free DNA integrity (cfDI), have great potential as diagnostic and prognostic markers in breast cancer patients. Here we investigated the potential prognostic ability of cfDNA conc and cfDI in a prospective study cohort of metastatic breast cancer (MBC) patients.

Methods: Blood was collected for cfDNA extraction from patients when enrolled about to start the first cycle of systematic therapy at baseline (MBCBL) and after the first cycle of systematic therapy (MBC1C). cfDNA conc and cfDI in blood plasma were evaluated by measuring the short and long fragments of two repetitive DNA elements, ALU (ALU-111bp, ALU-260bp) and LINE1 (LINE1-97bp, LINE1-266bp), by quantitative PCR. In total, 268 patients were included in this study. cfDNA conc and cfDI was compared between these two groups. The prognostic ability of cfDNA variables was evaluated by univariate and multivariate Cox regression model.

Results: A significant increase of cfDI (P = 1.21E-7 for ALU and P = 1.87E-3 for LINE1) and decrease of cfDNA conc (P = 1.17E-3 for ALU and P = 1.60E-2 for LINE1) were observed between patients at MBCBL and patients at MBC1C. Multiple Cox regression model indicated that cfDI and cfDNA conc can be used as independent prognostic markers in patients after one cycle of therapy with odds ratio (OR) and 95% confidence interval (CI) of 0.70 (0.48 - 1.01) for ALU cfDI, 0.63 (0.44 - 0.92) for LINE1 cfDI, 2.44 (1.68 - 3.53) for ALU cfDNA conc, 2.12 (1.47 - 3.06) for LINE1 cfDNA conc for overall survival. When four cfDNA variables were combined, it can reach an OR of 2.53 (1.77-3.62) for overall survival analysis of patients.

Conclusions: In summary, our results showed a decreased cfDNA conc and increased cfDI from the enrollment of the study to the first cycle of systematic therapy in MBC patients. cfDNA conc and cfDI can serve as independent prognostic markers in MBC patients after the first cycle of systematic therapy.

Legal entity responsible for the study: Molecular Biology of Breast Cancer, Department of Gynecology and Obstetrics, University of Heidelberg, Heidelberg, Germany

Funding: The University Hospital of Heidelberg, Heidelberg, Germany; the German Cancer Research Center (DKFZ), Heidelberg, Germany

Disclosure: All authors have declared no conflicts of interest.

282P Gene alteration in triple negative breast cancer patients in a phase I/II study of combination therapy with eribulin and olaparib

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Background: Olaparib (Lynparza®) shows efficacy in patients with triple negative breast cancer (TNBC). Eribulin is one of the standard therapies for metastatic breast cancer. A phase I/II study of combination therapy with eribulin and olaparib capsule (EO study) was conducted on patients with TNBC. We investigated the correlation between response to combination therapy and homologous recombination deficiency (HRD).

Methods: Tissue samples were collected from patients who participated in the EO study. Archival tissue samples were examined for gene alterations using the Foundation Medicine, Inc. (FMI) gene panel. Pathogenic or likely pathogenic gene alterations were extracted from all detected gene alterations using the FMI data dictionary. This dictionary uses the COSMIC database, relevant literature, and internal evidence to determine the reportable status of an alteration. HRD-related genes were defined as previously described (Konstantinopoulos PA, et al. Cancer Discovery, 2015). Correlation between presence of HRD and response to combination therapy was tested using chi-square test.

Results: A total of 32 tissue samples were collected. Nineteen samples were collected from the phase I and 13 samples from the phase II. Seventeen patients were treated at the recommended dose. Thirty-three gene mutations were detected. The most frequent gene mutations were *TP53* (n = 27, 84.4%), *PIK3CA* (n = 7, 21.9%), *BRCA1* (n = 5, 15.6%), *MLL3* (n = 5, 15.6%), and *AKT1* (n = 4, 12.5%). We detected 32 gene amplifications, with *MYC* being the most common (n = 6, 18.8%). Eight homozygous deletions were detected, and the most frequent was loss of *PTEN* (n = 4, 12.5%). We detected 10 gene rearrangements. HRD, including *BRCA1/2* mutations, was observed in nine patients. The overall response rate (RR) and clinical benefit rate (CBR) were 31.3% and 78.1%, respectively. The RRs in patients with HRD and without HRD were 44.4% and 26.1%, respectively (p=.4072). The CBRs for the HRD and non-HRD groups were 66.7% and 82.6%, respectively (p =.3702).

Conclusions: Eighty-three gene alterations were detected in TNBC pts receiving combination olaparib/eribulin therapy. Patients with HRD had numerically higher response rate.

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Legal entity responsible for the study: Japan

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283P Neutrophil-lymphocyte ratio (NLR) as a prognostic factor in metastatic breast cancer

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Background: Neutrophil-lymphocyte ratio (NLR) might be a surrogate marker of the tumor microenvironment immune balance and has been proposed as a prognostic factor for different tumors. A metanalysis of NLR for breast cancer (BC) showed that higher values at diagnosis were associated with lower survival. However, these results were mainly derived from the analysis of early BC cases: only three of twelve articles included women with metastatic breast cancer (MBC), sample size was small and no differential statistical analysis was performed for MBC. The aim of this work was to determine the prognostic value of NLR for MBC.

Methods: We retrospectively collected clinical and analytical data from a series of consecutive MBC patients treated in one center between 2009 and 2016. NLR (=neutrophil count/lymphocyte count) was obtained from differential white blood cell count at diagnosis of metastasis, before starting any treatment. Non-parametric tests (Mann Whitney U, Kruskal-Wallis) were used to evaluate differences of NLR between groups. Kaplan-Meier curves and Cox regression models (univariate and multivariate) were used for overall survival analysis.

Results: 265 consecutive patients with MBC were included, 117 of them (44%) with metastatic disease at diagnosis. Median age: 59 (19-95); ECOG 0-1 (69%), 2-3 (12%); site: bone only (37%), visceral only (18%), bone+visceral (30%); tumor subtype: HR (hormone receptor)+/HER2- (59%), HR+/HER2 + (17%), HR-/HER2 + (7%), HR-/HER2- (14%); disease free interval in recurrent MBC: <24 months (48, 32%), > 24 months (100, 67%). Outcomes: 135 deaths; median overall survival (OS): 35 months (IC95%: 27.4-42.6). Median NLR was 2.31 (range: 0.70-44.33), with significant higher values in women with ECOG 2-3 ($p = 0.008$) or negative estrogen receptors ($p = 0.03$). Univariate Cox model of OS showed a HR = 1.07 (95%: 1.03-1.11; $p < 0.001$) for NLR as a continuous variable; using the median value as cut-off, HR = 1.47 (95%CI: 1.05-2.07; $p = 0.024$). A multivariate Cox model showed the independent value of NLR for OS (Table).

Table: 283P Multivariate Cox proportional hazard regression model of MBC overall survival including NLR at diagnosis of distant disease

	HR (95%CI)	p
MBC at diagnosis (M1)	1.48 (1.02-2.14)	0.036
Negative estrogen receptors	2.56 (1.75-3.76)	<0.001
LNR (continuous variable)	1.07 (1.03-1.11)	0.001
Age (continuous variable)	1.02 (1.00-1.03)	0.008

Conclusions: A higher NLR at diagnosis is a negative prognostic factor for overall survival in metastatic breast cancer. These data, if prospectively validated, may support the addition of NLR to MBC prognostic models and may lead to differential therapeutic approaches in patients with higher NLR.

Legal entity responsible for the study: Francisco Ayala de la Peña

Funding: None

Disclosure: All authors have declared no conflicts of interest.

284P Real-life study of BRCA genetic screening in metastatic breast cancer

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Background: Genomic instability is a hallmark of cancers and mutations in the DNA repair BRCA1 and BRCA2 genes predispose to breast and other cancers. Prevalence of BRCA1/2 mutations is known in general population, but the frequency of these mutations in patients with metastatic breast cancer has not been established.

Methods: Prospective *BRCA1* and *BRCA2* genetic testing was proposed to all patients with metastatic breast cancer treated in 7 centers (in Franche-Comte, France) between February 19th 2015 and November 30th. *BRCA True™* test (Pathway Genomics®, San Diego CA, USA) was used to analyze the coding and flanking regions of *BRCA1* and *BRCA2* genes associated with hereditary breast and ovarian cancer by next-generation sequencing-base and Sanger sequencing.

Results: Of the 407 metastatic breast cancer patients, 11 (2.7%) had pathogenic germline BRCA1/2 mutations. BRCA2 (n = 8) mutations were the most frequent. Five of 11 patients (45%) would not have been candidate for BRCA1/2 mutation screening according to genetic counseling recommendations. All patients with a BRCA2 mutation presented a luminal metastatic breast cancer whereas all patients with BRCA1 mutation had a triple-negative metastatic breast cancer.

Conclusions: This is the first study assessing the prevalence of germline *BRCA1* and *BRCA2* mutations in an unselected population of patients with metastatic breast cancer. These patients with *BRCA1*/2 germline mutation represent the targeted population for poly(ADP-ribose) polymerase (PARP) inhibitors based therapy.

Legal entity responsible for the study: University Hospital Jean Minjoz of Besancon, France

Funding: BioMarin

Disclosure: All authors have declared no conflicts of interest.

285P Higher MCTS1 mRNA level in breast cancer may associate with an unfavorable outcome

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Background: The oncogene MCTS1 was originally discovered as an amplified product in a subset of T-cell lymphoma lines. It has been involved in cell cycle progression and conferring a growth advantage in lymphomas. However, the role of MCTS1 in predicting the outcome of breast cancer patients remains unclear.

Methods: GEPIA was a newly–developed web server for gene expression profiling and interactive analyses. We analyzed the gene expression profile across the clinical and RNA-seq data of 1085 breast cancer and 291 normal breast tissue based on TCGA and GTEx data.

Results: The results showed that MCTS1 was one of the most differential survival genes, and the median expression levels of MCST1 in breast cancer and normal tissue were 51.3 and 32.7 respectively. The overall survival of breast cancer patients with high MCTS1 mRNA level was inferior to that with low MCTS1 mRNA level (Logrank p = 2.3e−06). Cox Proportional Hazards Model analysis showed that MCST1 mRNA level in tumor was an independent predictor for overall survival status in breast cancer patients (HR = 2.2, p(HR)=4.1e−06). We inquired MCST1 on UCSC Genome Browser on Human Dec. 2013 (GRCh38/hg38) Assembly, and the result showed that H3K27ac, an active enhancer mark associated with the activation of transcription, was highly modified in promoter subdomain. We further analyzed the functional protein association networks on the String database, which showed that DENR involved in the translation of target mRNAs by recognizing the initiation codon were related to breast cancer with high MCTS1 mRNA expression.

Conclusions: In conclusion, higher MCTS1 mRNA level in breast cancer may associate with an unfavorable outcome due to H3K27ac modified MCTS1 promoter hyperacylation, which promotes its expression to inhibit apoptosis and cell cycle progression. To further confirm it, the experiment about the transfection of the shRNA on target gene is undergoing.

Legal entity responsible for the study: Guangdong Academy of Medical Sciences & Guangdong General Hospital, Guangzhou, China Guangdong Academy of Medical Sciences & Guangdong General Hospital, Guangzhou, China

Funding: None

Disclosure: All authors have declared no conflicts of interest.

286P Holistic therapeutic strategy of TNBC necessitates in depth molecular classification: A prospective study

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Background: Triple negative breast cancer (TNBC), the most heterogeneous and aggressive breast cancer has always remained a global burden. To understand the molecular pathogenesis, we stratified the seven subgroups of TNBC propounded by Lehmann et al (2011) as: [1] TNBC with alterations of the DNA damage repair and cell cycle checkpoint pathways (Basal Like 1 & 2 (BL1, BL2)), [2] with upregulation of cell signalling and cell motility pathways (mesenchymal (M), mesemchymal stem like (MSL)), [3] with upregulated cell survival pathways (BL2, M, MSL) [4] With upregulated angiogenesis pathways (BL2, MSL), [5] With upregulation of pathways associated with T cell signalling, [6] With upregulated Androgen receptor signalling pathways. Our objective was to prioritize the basic molecular heterogeneity of TNBC in redefining our choice of drugs.

Methods: Lehmann's TNBC subgroups showed deregulation of diverse molecular pathways necessitating targeted therapeutics. We conducted a Meta-Analysis on12

randomized reported trial cases (n = 1170), solely under the following classes of drug regimens: [1] DNA destabilizers, [2] PARP inhibitors, [3] Microtubule stabilizers, [4] Angiogenesis inhibitors, [5] Antimetabolite, [6] T cell targeted therapy; as single or combinational therapies. Radiotherapy recipients were excluded.

Results: Best therapeutic efficacies of DNA destabilizers with angiogenesis inhibitors in combination than monotherapy with either (OR: 5.011-7.286; p value< 0.001) indicated a significant prevalence of basal like TNBCs in populations. Statistical significance with antimetabolites as combination therapy (OR: 2.343; p value: 0.018) and not with microtubule stabilizer (OR: 0.377) were remarkable, indicating probability of less predominance of M or MSL type TNBC in a population. PARP inhibitors or T cell targeted therapies were also found promising (OR: 1.120, 1.040 respectively), warranting their targeted usage for BRCA1 deficient and IM type TNBCs respectively.

Conclusions: For TNBC treatment, personalized medicine and not a generalized treatment strategy should be considered.

Legal entity responsible for the study: Netaji Subhas Chandra Bose Cancer Research Institute

Funding: None

Disclosure: All authors have declared no conflicts of interest.

287P Neutrophil-to-lymphocyte ratio in metastatic breast cancer: Association with clinico-pathological features and outcome

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Background: Tumors are closely linked with systemic inflammation, of which neutrophil-to-lymphocyte ratio (NLR) represents a simple and inexpensive tool of evaluation. Previous data suggested that a high NLR is associated with poor prognosis in several tumors, including breast cancer (BC). However, few studies involved patients (pts) with metastatic breast cancer (mBC).

Methods: We retrospectively analyzed clinico-pathological features and treatment outcome of 595 consecutive mBC pts treated at the Department of Oncology of Udine, Italy, between 2004 and 2014. NLR was calculated from the blood count performed before first line therapy start. Differences in NLR according to clinico-pathological characteristics were investigated through chi-square test. Cox regression was used to determine the prognostic impact of NLR.

Results: A statistically significant higher NLR was found in pts whose tumor had the following features: high grade (P = 0.009), ductal isotype (P = 0.02), ER negativity (P = 0.003), PgR negativity (P = 0.0001), high Ki-67 (P = 0.03). There were no statistical differences in NLR between HER2-positive and HER2-negative BC (P = 0.33). Among subtypes, triple-negative BC were associated with higher NLR, while luminal HER2+ BC with lower NLR (P = 0.004). No statistical differences in NLR were found according to visceral disease (P = 0.13) nor according with bone-only disease (P = 0.24). At univariate analysis, a NLR $\geq$2.64 was associated with worse progression-free survival after first line therapy (HR 1.41, 95%CI 1.11-1.79, P = 0.005) and with worse overall survival (HR 1.76, 95%CI 1.32-2.36, P < 0.0001). The statistical significance was lost at multivariate analysis (P = 0.08 and P = 0.13, respectively). Of note, a subgroup analysis showed a significant prognostic value of NLR in HER2-positive subtype (HR 4.89, 95%CI 1.13-21.23).

Conclusions: High NLR was associated with pathological features of BC, but did not represent an independent prognostic factor at multivariate analysis. Further investigation is warranted to identify the appropriate cut-off value of NLR and the BC subtypes in which its prognostic role could be more useful.

Legal entity responsible for the study: University of Udine

Funding: None

Disclosure: All authors have declared no conflicts of interest.

288P Prognosis after loco-regional recurrence of breast cancer: 35 years longitudinal data from the Stockholm cancer register

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Background: Loco-regional recurrence (LRR) of breast cancer is a significant cause of morbidity and mortality. It is poorly described how prognosis after LRR has evolved over time at the population level.

Methods: 2272 patients diagnosed with LRR between 1980-2014 were identified within the Stockholm cancer registry and divided in 7 cohorts by the year of LRR diagnosis. Post-relapse event free survival (EFS) and overall survival (OS) were analyzed separately in local and loco-regional relapses and compared across the cohorts by Cox regression method. Primary tumor size, axillary node status, estrogen receptor (ER) status, type of surgery, adjuvant chemotherapy, LRR free survival, and age at LRR were the covariates for Cox model adjustment.

Results: In 1615 patients diagnosed with local relapse, 903 post-LRR events were registered (Table). A significant improvement in median EFS (p < .001) and OS (p < .001) was observed in patients diagnosed 2010-14 compared with previous time periods. Among 657 patients with loco-regional recurrences, 476 experienced a post-LRR event (Table). EFS and OS independently improved over time (p <.001 and p <.001, respectively). Smaller primary tumors, negative axillary lymph nodes, ER positive status, breast-conserving surgery, longer LRR-free interval and younger age at LRR occurrence were independently associated with longer survival after LRR. No association was observed between survival and type of surgery or LRR-free interval in LRRs. An improvement in survival over time was also demostrated when cohorts 1980-84 and 2010-14 were excluded from the model.

Table: 288P

	Local recurrence	Locoregional recurrence
Type of post-lLRR relapse	N (%)	N (%)
Loco-regional	117 (13%)	57 (12%)
Distant	438 (49%)	305 (64%)
Loco-regional + distant	13 (1%)	3 (1%)
Death	335 (37%)	111 (23%)
Total	903 (100%)	476 (100%)

Conclusions: Survival after LRR has gradually improved over the last 35 years regardless of other recognized prognostic factors.

Legal entity responsible for the study: Karolinska Institutet

Funding: Dagmar Ferbsminnesfond

Disclosure: All authors have declared no conflicts of interest.

289P The CAN BEAR study: A systematic review and meta-analysis investigating adverse events (AEs) of targeted agents added to endocrine therapy (ET) in patients (pts) with hormone-receptor positive (HR+) metastatic breast cancer (MBC)

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Background: Combining targeted agents and ET improves outcomes in pts with HR+ MBC but increases the risk of AEs. However, the specific additional toxicity burden caused by these agents remains unknown. Our meta-analysis aims to better estimate the comparative risk of AEs with the combination of ET and CDK4/6 inhibitors, PI3K inhibitors, mTOR inhibitors and anti-HER2 agents in pts with HR+ MBC.

Methods: A systematic literature search of MEDLINE, EMBASE, Cochrane Library and proceedings from major conferences up to March 31st 2017 was conducted to identify randomized controlled trials investigating ET plus CDK4/6, PI3K, mTOR inhibitors and anti-HER2 agents as compared to ET alone in pts with HR+ MBC. For each class of targeted agents, two groups were considered: ET plus targeted agent vs. ET alone. Summary risk estimates (odds ratio, OR) and 95% confidence intervals (CI) were calculated for each side effect within each class of targeted agents for each trial. Pooled analysis was conducted using the random and fixed effects models.

Results: A total of 7865 pts from 15 studies were included in our meta-analysis. Overall, the addition of targeted agents to ET was associated with significant higher risk of grade 3-4 AEs: OR 2.95 (95% CI 2.47-3.53) for CDK4/6 inhibitors, 2.05 (95% CI 1.63-2.58) for PI3K inhibitors, 1.89 (95% CI 1.40-2.56) for mTOR inhibitors, and 2.33 (95% CI 1.17-4.63) for anti-HER2 agents. Anti-HER2 agents, CDK4/6 and PI3K inhibitors significantly increased the risk of grade 3-4 fatigue, but not mTOR inhibitors (OR 1.48; 95% CI 0.64-3.43). Anti-HER2 agents, PI3K and mTOR inhibitors significantly increased the risk of grade 3-4 diarrhea, but not CDK4/6 inhibitors (OR 1.15; 95% CI 0.46-2.87). Other AEs and class specific toxicities will be reported at the conference.

Conclusions: In pts with HR+ MBC, the combination of targeted agents and ET is associated with significant increased risk of AEs. The risk of developing different AEs varies largely according to the type of agent used. Potential specific toxicities should be taken into account and discussed with patients when deciding to opt for combination regimens.

Clinical trial identification: PROSPERO registration number: CRD42017058278

Legal entity responsible for the study: Samuel Martel

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Disclosure: E. De Azambuja: Honoraria from Roche and travel grants from Roche and GlaxoSmithKline outside the submitted work. All other authors have declared no conflicts of interest.

290P OlympiAD: Health-related quality of life (HRQoL) in patients with HER2-negative metastatic breast cancer (mBC) and a germline BRCA mutation (gBRCAm) receiving olaparib monotherapy vs standard single-agent chemotherapy treatment of physician's choice (TPC)

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Background: The Phase III OlympiAD study showed a statistically significant and clinically meaningful PFS survival benefit with olaparib monotherapy, compared with standard of care chemotherapy (median 7.0 vs 4.2 months, respectively, hazard ratio 0.58; 95% CI 0.43, 0.80; $P = 0.0009$) in patients (pts) with HER2-negative mBC and a g*BRCAm*. A key predefined secondary objective was to assess the effect of olaparib on HRQoL.

Methods: The randomized, open-label, Phase III OlympiAD study (NCT02000622) enrolled pts with HER2-negative mBC and a g*BRCA*m, after ≤2 chemotherapy lines for mBC. Pts were randomized 2:1 to olaparib tablets (300 mg bid) or single-agent treatment of physician's choice (TPC; capecitabine, vinorelbine or eribulin). Pts were asked to complete an EORTC QLQ-C30 questionnaire (analysis focused on the Global HRQoL scale with range 0–100, and higher scores indicating a better QoL), at baseline and every 6 weeks until disease progression. Changes in Global HRQoL scores were analyzed descriptively, and mean change from baseline (cfb) by a mixed model for repeated measures.

Results: 302 pts (ITT) were randomized to olaparib (n = 205) or TPC (n = 97). Overall QLQ-C30 compliance rate was 93% for olaparib vs 77% for TPC. HRQoL was better preserved with olaparib than TPC (mean cfb in Global HRQoL score across all visits was 3.9 [n = 191] vs -3.6 [n = 73], respectively, difference 7.5; 95% CI 2.48, 12.44; P=0.0035). The proportion of pts (ITT) who were free of Global HRQoL deterioration (cfb decrease in ≥ 10 points) was 81.5% in the olaparib arm vs 61.2% in the TPC arm at 6 months, and 64.0% vs 53.5% at 12 months, respectively. The median time to Global HRQoL deterioration was not reached in olaparib pts, and was 15.3 months for TPC pts. A best HRQoL response of 'improved' (cfb increase in ≥ 10 points over two visits ≥21 days apart) was observed in 34% olaparib pts vs 13% TPC.

Conclusions: Pts receiving olaparib experienced significantly less and later deterioration in Global HRQoL vs TPC. HRQoL was modestly and consistently greater in patients receiving olaparib compared with TPC.

Clinical trial identification: Clinical trials no: NCT02000622

Release date: 18 November 2013

AstraZeneca name: OlympiAD

AstraZeneca number: D0819C00003.

Legal entity responsible for the study: AstraZeneca

Funding: AstraZeneca

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291P PALOMA-2: Neutropenia (NP) patterns in patients (Pts) with estrogen receptor−positive (ER+)/human epidermal growth factor receptor 2−negative (HER2–) first-line advanced breast cancer (ABC) receiving palbociclib + letrozole (P+L)

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Background: PALOMA-2 demonstrated efficacy of P+L vs placebo (PBO) + L in pts with treatment-naive ER+/HER2– ABC (Finn *NEJM* 2016). We describe clinical patterns of hematologic adverse events (AEs), with an emphasis on NP, in pts receiving P+L.

Methods: Postmenopausal women (N = 666) with no prior systemic therapy for ABC were randomized 2:1 to receive P+L (P, 125 mg/d, 3 wk on/1 wk off; L, 2.5 mg/d continuously) or PBO+L (L, 2.5 mg/d continuously) until disease progression, unacceptable toxicity, or consent withdrawal. Hematological AEs are reported based on lab results.

Results: As of 2/26/2016, median follow-up was 23.0 mo in pts receiving P+L (n = 444). Median age of P+L pts was 62.0 (range, 30–89) years; ECOG status was 0, 1, and 2 in 57.9%, 40.1%, and 2.0%, respectively; and 213 (48.0%) received prior chemotherapy. 423 (95.3%) P+L pts experienced any grade (gr) NP, including 298 (70.4%) with gr 3/4 NP, manageable with dose modification. Among pts with gr 3/4 NP, 65 (15.4%), 41 (9.7%), and 192 (45.4%) experienced 1, 2, or ≥ 3 episodes, respectively. 92 (20.7%) and 84 (18.9%) pts experienced 3–5 episodes of any grade anemia and thrombocytopenia, respectively. Median (range) times to first episode of gr ≥ 3 NP, anemia, and thrombocytopenia were 28.0 d (12 − 854 [median duration, 31.5]), 182.0 d (14 − 760 [11.5]), and 283.5 d (21 − 617 [26.5]), respectively. Although NP is associated with increased risk of infection, the rate of gr 3/4 infections was 3.5% in P+L pts with NP. Of pts with gr 3/4 NP, 68.8% did not have any overlapping infections. Febrile NP was reported in 1.8% of P+L pts and did not result in therapy discontinuation. In univariate analysis, risk of developing gr 3/4 NP was associated with Asian ethnicity (P=0.0002) and low baseline absolute neutrophil counts (P<0.0001). NP resulting in dose reduction or interruption had no impact on PFS.

Conclusions: NP occurred early during therapy, and was manageable with dose modification. Febrile NP was reported in 1.8% of P+L pts and did not result in therapy discontinuation. Withholding dose, or dose reduction does not negatively impact PFS.

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Clinical trial identification: NCT01740427

Legal entity responsible for the study: Pfizer Inc

Funding: Pfizer Inc

Disclosure: V. Diéras: Consulting and advisory role: Genentech, Lilly, Pfizer, AbbVie, Novartis Pharma KK, Roche-Peru. Speakers bureau: Pfizer, Novartis Pharma KK, Roche-Peru. N. Harbeck: Honoraria: Lilly, Novartis, Pfizer. A.A. Joy: Honoraria: Pfizer, Novartis, Roche, Eli Lilly, AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim. Consulting or Advisory: Pfizer, Novartis, Roche, Eli Lilly, AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim. K.A. Gelmon: Consulting or Advisory Role: Pfizer, Novartis, AstraZeneca, NanoString Technologies, Merck. J. Ettl: Honoraria: Pfizer, Novartis Pharma KK, Roche-Peru. Consulting or advisory role: Pfizer, Novartis Pharma KK. Speakers bureau: Pfizer, Novartis Pharma KK, Roche KK. S. Verma: Consulting and advisory role: Genentech/Roche, Lilly, Pfizer, Novartis, Amgen. D. Lu, E.R. Gauthier, P. Schnell, A. Mori: Pfizer employee and shareholder. H.S. Rugo: Speakers bureau and honoraria: Genomic Health. Research funding: Plexxikon Macrogenics, OBI Pharma, Eisai, Pfizer, Novartis, Lilly, GlaxoSmithKline, Genentech, Celsion, Merck, Clovis Oncology. 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.

292P Prospective observational study of peripheral neuropathy in breast cancer patients treated with eribulin

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Background: Eribulin mesylate (ERI), a nontaxane microtubule dynamics inhibitor, has antitumor activity and can prolong overall survival in patients with recurrent breast cancer (BC). As data lack on peripheral neuropathy (PN) when using ERI as primary or

secondary therapy for recurrent BC, we assessed the incidence of PN, the times to PN onset and recovery, and the risk factors for PN in patients with HER-2-negative recurrent or metastatic BC treated with ERI.

Methods: We analyzed data from an ongoing 2-year multicenter prospective observational study where the same number of patients who started ERI administration as primary or secondary therapy and as tertiary or later therapy were enrolled. PN events were defined as new onset or existing PN worsened after ERI administration. Logistic regression was run to assess the risk factors.

Results: The analysis set comprised 458 patients who had completed 6-month follow-up after ERI administration. Mean age ± standard deviation was 59.4 ± 10.9 years, and 171 patients (37.3%) had a history of PN from previous chemotherapy and 190 (41.5%) had existing PN at start of ERI administration (baseline). PN events were observed in 115 patients (25.1%), with severity of Grade 1 in 55 (12.0%), Grade 2 in 51 (11.1%), and Grade 3 in 9 (2.0%) in accordance with the Common Terminology Criteria for Adverse Events version 4.0. After the PN events, 91 patients (79.1%) continued ERI, and 16 (13.9%) reduced the dose or underwent a drug holiday. Within 6 months after ERI administration, 39.0% recovered to the state at baseline. In 266 patients without PN at baseline, new PN appeared in 71 patients (26.7%), and median time to PN onset was 57.0 days (95% confidence interval, 43.0–66.0 days). Results also showed that "history of radiotherapy", "hemoglobin level", and "history of PN from previous chemotherapy" were significantly associated with PN events, but no evident association was found with the number of chemotherapy prior to baseline.

Conclusions: PN events were observed in about one-quarter of patients treated with ERI, most of which were mild, and about one-third of patients who developed PN recovered early. This suggests that ERI is well tolerated.

Clinical trial identification: NCT02371174 (First release on November 21, 2014)

Legal entity responsible for the study: NA

Funding: Eisai Co., Ltd., Tokyo, Japan

Disclosure: Y. Sakata, H. Iwata, H. Ikezawa, R. Fudetani, D. Tonoda, Y. Uchida, H. Hasegawa, T. Matsuoka: Employee of Eisai Co., Ltd.

293P Overall survival and quality of life in patients with metastatic breast cancer treated with nab-paclitaxel: Final results of the non-interventional study NABUCCO

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Background: Nab-paclitaxel (Nab-P) is approved for the treatment of metastatic breast cancer (MBC) after first line therapy and when anthracyclines are not indicated. Clinical trials proved high efficacy and reduced toxicity of nab-P compared to standard taxanes. Real world data of nab-P in MBC, however, are still limited.

Methods: The prospective, multicenter, non-interventional NABUCCO study was designed to collect data on effectiveness including overall survival, safety, treatment patterns and quality of life (QoL) in patients (pts) with MBC in real world. QoL was assessed with the validated questionnaires Functional Assessment of Cancer Therapy-General (FACT-G) and the breast cancer and taxane specific modules (FACT-B and FACT-Taxane) at baseline (BL), 3, 6 months. Data were analyzed descriptively. Survival was analyzed with the Kaplan-Meier method.

Results: 697 of 705 pts with MBC enrolled at 128 sites in Germany from 4/2012 to 4/2015 were evaluable (median age 62.3 years (yrs) (min-max 29.2-89.3); age ≥65 yrs n = 291 (41.8%), ECOG 0/1 n = 628 (90.1%), prior taxanes n = 419 (60.1%)). 194 pts (27.8%) received 220-260 mg/m^2 q3w, 491 pts (70.4%) received weekly *nab*-P at ≤ 150 mg/m^2 (physician's discretion; 1.7% other). Median overall survival (mOS, months [95% CI]) was 15.6 [14.2-17.2]. No difference was observed with regard to treatment pattern (15.1 [12.3-17.5] q3w vs 16.3 [14.4-18.5] weekly) and age (15.7 [14.0-18.1] <65 yrs vs 15.1 [12.8 - 17.3] ≥ 65 yrs). mOS was significantly shorter in pts receiving prior taxanes (13.7 [11.7-15.5] vs. 18.3 [16.4-22.2]) or prior chemotherapy in general (19.2 [16.9-22.2], 15.1 [12.5-17.3], 14.1 [10.3-17.2], 11.3 [9.1-12.7] with 0, 1, 2, ≥ 3 prior palliative lines). Consistent with safety data, pts reported increased taxane-related symptoms after start of *nab*-P (BL vs 6 months; [range]: FACT-Taxane subscale score 52.3 [4.0-64.0] vs 40.0 [3.0-64.0]). Global and breast cancer related QoL were not affected (FACT-G 71.3 [27.0-105.0] vs 67.0 [14.0-104.0]; FACT-B subscale score 23.6 [0.0-35.0] vs 22.0 [2.0-35.0]).

Conclusions: The NABUCCO study confirms survival data from clinical trials in real world without deteriorated global and breast cancer related QoL.

Clinical trial identification: IOM-02240

Legal entity responsible for the study: iOMEDICO AG

Funding: Celgene

Disclosure: All authors have declared no conflicts of interest.

294P Assessment of gastric pH changes and food intake on ribociclib bioavailability: In silico and clinical evaluations

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Background: Ribociclib (KISQALI®) is a CDK4/6 inhibitor that has been approved recently in the United States for use in combination with an aromatase inhibitor as a first-line therapy for HR+, HER2− advanced or metastatic breast cancer. The recommended ribociclib dose is 600 mg/day (3-weeks-on/1-week-off) with no restrictions on food intake or concomitant proton pump inhibitor (PPI) use. Here we examine the influence of gastric pH and food intake on ribociclib bioavailability using physiology-based pharmacokinetics (PBPK) modelling, observed clinical pharmacokinetic (PK) data, and population PK (pop-PK) analysis.

Methods: *In silico* PBPK models based on *in vitro* and preclinical data were built and fitted with clinical PK data from healthy volunteers. Sensitivity analyses were performed to evaluate the effect of gastric pH (range, 0.5-8.0) on ribociclib PK and absorption. A descriptive statistical analysis of clinical PK data from patients with and without concomitant PPI use and a pop-PK analysis were used to examine the effect of PPI dose

Table: 294P Ribociclib PK parameters by PPI use[a]

Study No.	PK Parameter	n	PPI Use	Geometric Mean (Geometric Coefficient of Variation, %)
X2107	$AUC_{0\text{-}24h}$ (ng*hr/mL)	8	Yes	24,700 (30.6)
		10	No	21,100 (57.2)
	C_{max} (ng/mL)	10	Yes	1,780 (34.6)
		13	No	1,620 (53.2)
X2101	$AUC_{0\text{-}24h}$ (ng*hr/mL)	12	Yes	25,900 (79.1)
		46	No	23,700 (61.3)
	C_{max} (ng/mL)	13	Yes	2,050 (74.7)
		48	No	1,870 (60.3)
X1101	$AUC_{0\text{-}24h}$ (ng*hr/mL)	2	Yes	42,600 (28.7)
		6	No	55,100 (68.6)
	C_{max} (ng/mL)	2	Yes	2,700 (53.0)
		6	No	3,500 (65.8)

$AUC_{0\text{-}24h}$, area under the concentration-time curve from time zero to 24 hours; C_{max}, maximal concentration; PK, pharmacokinetics; PPI, proton pump inhibitor. [a]Defined by PPI use prior to and on the day of sampling on C1D15 for $AUC_{0\text{-}24h}$ and C_{max}, and on the dosing date corresponding to the $AUC_{0\text{-}24h}$ or C_{max}. "Yes" was defined as PPI use for at least 5 consecutive days; "No" was defined as no PPIs use for at least 13 consecutive days.

intensity on ribociclib bioavailability. The effect of a high-fat meal on ribociclib exposure was evaluated in a bioequivalence trial in healthy volunteers.

Results: Sensitivity analyses using validated PBPK models predicted no effect of varying stomach pH on ribociclib absorption. PK data ($AUC_{0\text{-}24h}$ and C_{max}) from several clinical studies showed similar ribociclib exposure regardless of PPI use (Table). The pop-PK analysis supported the PBPK models and clinical findings by showing that PPI use is a statistically insignificant and clinically unimportant covariate on ribociclib bioavailability. Food intake did not affect the rate or extent of ribociclib absorption.

Conclusions: *In silico* models and clinical PK data indicate that ribociclib can be administered without regard to PPI use or food intake. This lack of dosing restriction may facilitate greater patient compliance and clinical benefit.

Legal entity responsible for the study: Novartis Pharmaceuticals Corporation

Funding: Novartis Pharmaceuticals Corporation

Disclosure: T. Samant, M. Elmeliegy, Y. Lu, S. Yang, M. Miller, C. Germa: Employee of Novartis Pharmaceuticals Corporation. S. Dhuria: Was an employee Novartis Pharmaceuticals Corporation at the time this study was conducted; currently a consultant for Novartis Pharmaceuticals Corporation. M. Laisney, A. Grandeury, M. Mueller-Zsigmondy, K-I. Umehara, F. Huth: Employee of Novartis Pharma AG.

295P Pneumocystis jiroveci pneumonia (PCP) in patients receiving weekly chemotherapy for metastatic breast cancer

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Background: Pneumocystis jiroveci pneumonia (PCP) is thought to be a rare phenomenon in the solid tumour population, particularly in patients with breast cancer. However, it may be increasing within this population as the type and intensity of chemotherapy used changes. There is currently a lack of consensus on PCP prophylaxis in patients who are immunocompromised due to chemotherapy.

Methods: The EPIC electronic health record system was searched for metastatic breast cancer (MBC) patients treated with a weekly chemotherapy (epirubicin/paclitaxel) regimen from October 2014 – February 2016 at Addenbrooke's hospital (n = 49). A subset of patients diagnosed with PCP (n = 5) was identified. A retrospective analysis was performed on the charts of all patients.

Results: Patients received a mean of 21 weeks (SD = 15, min=1, max=62) of chemotherapy. An overall of 16% (n = 8) of patients had profound lymphopaenia (absolute lymphocyte count $<0.5*10^9$/L) at some point during their treatment. 10% (n = 5) of the patients were diagnosed with confirmed (n = 3) and probable (n = 2) PCP.

Conclusions: A high incidence of PCP was observed in MBC patients receiving weekly epirubicin/paclitaxel treatment. Additional investigation is needed to define the population of patients at the greatest risk of PCP infection, and to identify those who might benefit from antibiotic prophylaxis.

Legal entity responsible for the study: Cambridge Cancer Centre

Funding: None

Disclosure: All authors have declared no conflicts of interest.

296P Detection of early cardiac effects of docetaxel plus trastuzumab and pertuzumab through strain rate imaging in patients with HER2-positive metastatic breast cancer

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Background: Dual anti- HER2 therapy with trastuzumab and pertuzumab in combination with taxane-based chemotherapy improves overall survival in patients with metastatic HER2-positive breast cancer. There is a critical need to investigate the potential cardiotoxicity of dual anti-HER2 blockade, given the importance of HER2 signaling in cardiac homeostasis and stress response. Sequential left ventricular (LV) ejection fraction (EF) assessment has been mandated to detect myocardial dysfunction. Changes in cardiac function induced by this therapy, however, are subtle and difficult to quantitate by conventional imaging methods. Doppler myocardial imaging-based velocity, strain, and strain rate measurements have been shown to sensitively quantify abnormalities in cardiac function in other settings. The aim of this study was to determine if sensitive indices of left ventricular (LV) dysfunction, specifically strain rate imaging, would be useful for addressing the early detection of dual anti-HER2 mediated cardiotoxicity.

Methods: Patients with 0-1 lines of prior therapy were treated with 8 cycles of docetaxel (75mg/m(2) plus trastuzumab (8 mg/kg loading dose followed by 6 mg/kg) and pertuzumab (840 mg loading dose followed by 420 mg every 3 weeks. Conventional and Doppler myocardial imaging echocardiography were obtained at baseline and every 2 cycles of treatment. Segmental peak systolic longitudinal and radial velocity, strain, and strain rate (SR) were measured.

Results: Twenty-seven women (median age 52.2 years) were enrolled in the study. There was no overall change in Left ventricular dimensions, ejection fraction, and systolic myocardial velocity. In contrast, a significant reduction in longitudinal and radial strain and strain rate was found after 8 cycles (longitudinal strain -12.8% +/- 2.2% vs baseline (P = .001); radial strain 29.3% +/- 7.1% vs 50.3% +/- 10.6%, P < .001 vs baseline). Changes in radial function appeared earlier and were more pronounced than in longitudinal direction.

Conclusions: In contrast with conventional echocardiography myocardial velocity measurements allowed detecting subtle changes in longitudinal and radial left ventricular function after 8 cycles of therapy. We suggest that strain rate imaging identifies preclinical myocardial dysfunction earlier than conventional measures in women undergoing treatment with dual anti-HER2 therapy for metastatic breast cancer and could be used for cardiac function monitoring.

Legal entity responsible for the study: Vasiliki Michalaki

Funding: None

Disclosure: All authors have declared no conflicts of interest.

297P Evaluation of drug-drug interactions (DDI) between tucatinib and capecitabine (C) in patients with advanced HER2+ metastatic breast cancer from a phase 1b study

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Background: Tucatinib is an orally bioavailable, potent HER2 selective tyrosine kinase inhibitor. Based on the combination activity with chemotherapy and trastuzumab (Tz) in preclinical HER2+ tumor models, tucatinib was evaluated in combination with C and Tz in a Phase 1b study in patients with HER2+ metastatic breast cancer (mBC).

Methods: A phase 1b 3 + 3 dose escalation study (ONT-380-005) was conducted to evaluate the safety and tolerability of tucatinib in combination with C and Tz. Tucatinib (300 mg PO BID), C (1000 mg/m2 PO BID 14 days of a 21-day cycle), and Tz (8 mg/kg IV loading; then 6 mg/kg IV once every 21 days), were administered to HER2+ mBC patients previously treated with Tz and T-DM1. Pharmacokinetic (PK) assessments were conducted on cycle 1 day 14 (+C) and on cycle 1 day 21 (-C). PK of C and its major catabolites/metabolites were also measured. In vitro assessments of the activation of C were determined in the presence of tucatinib. The enzymes evaluated were carboxyesterase (CES), cytidine deaminase (CDA), thymidine phosphorylase (TP), and dihydropyrimidinephosphorylase (DPD).

Results: Tucatinib did not inhibit conversion of C to 5'-DFCR in vitro; at 10 μM tucatinib reduced ~30% of CES activity. Similarly, tucatinib did not have any significant effect on the activity of CDA, TP, or DPD. Results from *in vitro* inhibition studies suggested tucatinib does not have a measurable effect on the conversion of C to its active antimetabolite. The clinical PK of tucatinib was unchanged in the presence or absence of C. The PK of C and its catabolites/metabolites were also unaffected in the presence of tucatinib, and were consistent with reported literature.

Conclusions: The overall in vitro and clinical results indicate there is no evidence for DDI between tucatinib and C, including when the combination is given with Tz. The tucatinib-Tz-C triplet combination has been reported to be well tolerated and supports the evaluation of the efficacy of the combination regimen in an ongoing controlled, randomized, double-blinded registrational study (HER2CLIMB).

Clinical trial identification: ONT-380-005

Legal entity responsible for the study: Cascadian Therapeutics, Inc.

Funding: Cascadian Therapeutics, Inc.

Disclosure: A. Vo, D. Leviten, T. Sierra, A. Dozier, L. Walker, S. Peterson: Minor stockholder and employee of Cascadian Therapeutics, Inc. M. Insko: Minor stockholder of Cascadian Therapeutics, Inc., BLPH, and Faraday Pharmaceuticals Inc. Employee of Faraday Pharmaceuticals Inc.

298P Outcomes of intracranial stereotactic radiotherapy (SRT) in metastatic breast cancer (BC)

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Background: Brain metastases (BM) are a significant cause of morbidity and mortality. Advancement of systemic therapies for patients with BC has improved control of extracranial metastases and survival. Intracranial control however continues to be challenging. SRT has been shown to provide excellent local control (LC) with minimal toxicity, although breast specific data is comparatively lacking.

Methods: This study aims to describe outcomes of first SRT including LC, distant brain control (DC), time to intracranial progression (TTP) and overall survival (OS) in a cohort of patients with BC who received SRT from 2001 to 2016 at the Royal Marsden Hospital. Kaplan Meier and log-rank methods were used for statistical analysis.

Results: 64 patients underwent SRT for 129 BM. Median age was 52.4 years. 58 (91%) were ECOG 0/1. 18 (28%) were hormone receptor positive (HR+)/HER-2 negative, 38 (59%) were HER-2 enriched (HER-2+), and 8 (13%) were triple negative (TN). The median number of BM treated with SRT was 1 (range 1 - 12). Median dose and range was 20 Gy (12 – 35 Gy) in 1 fraction (1 – 10). 29 (45%) were treated using a linear

accelerator, 34 (53%) with CyberKnife and 1 with GammaKnife. 27 (42%) had prior whole or partial brain radiotherapy (WBRT). 21 (33%) had prior surgery. 30 (49%) had concurrent endocrine therapy, 25 (40%) had targeted therapy and 8 (13%) had chemotherapy. Follow-up imaging was available for 57 patients. Median follow up was 15 months. 1 year LC was 54% and DC was 56%. Median TTP was 7.1 months (95%CI: 6.1 – 10.8) and was significantly worse for TN compared to HER-2+ patients (5.3 vs 9.9 months, $p = 0.046$). Salvage radiotherapy or surgery was performed after SRT in 13 (23%) patients for local failure, and 20 (35%) for distant failure. 7 (12%) patients had radionecrosis following SRT. OS from SRT was 19.6 months (95%CI: 14.9 – 23.1), and was significantly worse for TN patients (13.6 vs 22.1 months, $p = 0.003$), age $\geq$ 60 years (14.9 vs 19.8 months, $p = 0.028$) and multiple brain metastases (14.0 vs 22.6 months, $p = 0.010$).

Conclusions: Outcomes in patients with BC and BM treated with SRT are excellent overall. Outcomes are worse in TN disease, older patients and patients with multiple BM, and should be considered in SRT decision making.

Legal entity responsible for the study: The Royal Marsden NHS Foundation Trust

Funding: The Royal Marsden NHS Foundation Trust/Ross Smith Cridlan Trust

Disclosure: All authors have declared no conflicts of interest.

299P Eribulin is safe and efficient in metastatic breast cancer in elderly patients. Results from the REPROLINE multicentric retro-prospective cohort

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Background: Treating metastatic breast cancer (MBC) in women of 70 years old or more is a frequent problem however few data are available describing the safety and efficacy of chemotherapy in elderly patients. Eribulin is validated for MBC from the 2nd line treatment onwards since two phase III studies. We present here a focus on safety and efficacy of eribulin in patients $\geq$ 70 years old compared to the results of younger patients in a real life cohort.

Methods: From Oct 2014 to Feb 2017, a multicentric retro-prospective study (REPROLINE) was conducted. Data concerning patient, tumor characteristics, previous treatments administered, tolerance, efficacy and outcome of eribulin were retrieved for patients treated in real life for MBC in 12 different French hospitals between Dec 2013 and Jan 2016. Data from 446 MBC patients were collected. This database was splitted in two cohorts: comparing the results from the cohort of 363 patients $<$ 70 years old (group A) to the cohort of 83 patients $\geq$70 years old or more (group B).

Results: Median age for each cohort was 56.3 and 75.4 years old. Both cohorts had similar tumour characteristics, number of metastatic sites and the median number of prior chemotherapy lines was 2. Albumine serum levels were lower in the group B with 21% of patients with albumine $<$ 30g/L versus 13% in group A, without any statistical difference. Outcomes were similar in group A and B with respectively: median PFS of 3.67 months versus 3.7 months; HR 0.972(CI 95% 0.762-1.241), $p = 0.821$. median OS 10.7 months vs 10.7 months; HR 0.997 (CI95% 0.752-1.323), $p = 0.984$. Patients in both groups received a median number of 4 cycles. The most frequent grade 3 adverse events were neutropenia (22.9% in group A and 15.7% in group B), fatigue (6.5% group A and 13.3% group B) and neurotoxicity (4.4% and 3.6%, respectively). No statistical difference between elderly and younger patients was demonstrated. 9.6% of the total patients stopped the treatment due to fatigue.

Conclusions: We present here the first study focusing retro-prospectively on the tolerance and efficacy of eribulin in elderly patients in real life. In this study, eribulin in patients $\geq$70 years old is as effective and safe as in younger patients.

Clinical trial identification: NCT02393287

Legal entity responsible for the study: Anne Patsouris

Funding: EISAI

Disclosure: All authors have declared no conflicts of interest.

300P Long-term responders to trastuzumab monotherapy in the first-line metastatic setting: characteristics and survival data (SAKK 22/99 Trial)

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Background: The prospective randomized trial SAKK 22/99 compared first-line trastuzumab plus chemotherapy with the sequential use of trastuzumab followed by chemotherapy plus trastuzumab at progression in patients with stage 4 HER2-positive breast cancer. The main results were recently published in Annals of Oncology. Here we report characteristics and outcomes of patients with long-lasting disease control with trastuzumab alone.

Methods: Long-term responders to trastuzumab monotherapy were defined as patients achieving disease control for $\geq$ 6 months. A risk score was defined as sum of negative prognostic factors (NPFs): ER negative (neg), PgR neg and visceral disease. The HER2:CEP17 FISH ratio was correlated with duration of response. Standard descriptive statistics were used. Survival analysis was done using the Kaplan-Meier method.

Results: Of 175 enrolled pts, 86 were randomised to receive trastuzumab monotherapy until PD. 24 patients (28%) were long-term responders ($\geq$6 months). In a landmark analysis excluding patients who died within 6 months, 5y-overall survival (OS) in long-term responders was 54% (95% CI 31–72) compared to 18% (95% CI 10–30) in short-term responders (log-rank $p = 0.02$). Baseline characteristics were well-balanced except for visceral disease (see Table, Fisher's exact test $p = 0.01$). With each additional NPF the proportion of long-term responders decreased: 0 NPF, 42%; 1 NPF, 40%; 2 NPFs, 35%; 3 NPFs 17%. Median FISH ratio was 4.8 (IQR 4.1–5.3) in long-term responders and 4.7 (IQR 2.5–5.3) in short-term responders; no long-term responders were in the lowest quartile of all FISH ratios.

Table: 300P Baseline characteristics

	HER2-long Responders (N = 24)	HER2-short Responders (N = 62)
Age (med)	57 years	52 years
Visceral disease (yes)	46%	76%
ER-Status (pos)	59%	60%
PR-Status (pos)	48%	41%
FISH (med. Ratio)	4.8	4.7
ALP U/l (med)	74	103
Hb g/l (med)	130	134
WBC G/l (med)	5.8	6.8
Endocrine treatment adj (yes)	33%	48%

Conclusions: Long response to trastuzumab monotherapy is prognostic with significantly higher 5y-survival rates in this cohort. Negative prognostic factors including lower FISH ratio may reduce the chance for long-term response to trastuzumab monotherapy as first line therapy.

Clinical trial identification: Subanalysis of SAKK 22/99 trial; NCT00004935

Legal entity responsible for the study: Swiss Group of Clinical Cancer Research (SAKK)

Funding: None

Disclosure: All authors have declared no conflicts of interest.

301P Metronomic chemotherapy (mCHT) in HER2-ve advanced breast cancer (ABC) patients (pts): Old drugs, new opportunities Preliminary results of the VICTOR-6 study

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Background: mCHT is the minimum biologically effective dose of a chemotherapeutic agent, given at regular dosing regimen with no prolonged drug free interval, that leads to anti-tumor activity. Old regimens included Cyclophosphamide-Methotrexate (CM), whereas in the last years new regimens, such as Vinorelbine (VRL) and Capecitabine (CAPE)-based have been developed. Aim of this observational retrospective ongoing study is to describe the use of mCHT in ABC pts across 5 years and the clinical characteristics of the pts together with efficacy of old (CM-like) vs new (VRL/CAPE-based) metronomic regimens in terms of response and disease control.

Methods: We retrospectively identified from clinical records those HER2-ve ABC pts who have received any kind of mCHT in the years 2011-2015, alone, or in combination with a non-metronomic drug. Standard statistical approaches were used for describing the sample characteristics. Logistic and non proportional hazard analysis were used to identify factors associated with response, and time to treatment failure and survival, respectively. This preliminary analysis focuses on Response Rate (RR) and Disease Control Rate (DCR).

Results: From June 2011 to December 2015, 267 pts have been identified till now and 233 are fully evaluable. Median age at mCHT start was 67 years. 81% was HR+ and 33% had non-visceral metastatic disease. 22% of the pts received CM, 55% VRL-based and 23% mCAPE-based regimens. mCHT use increased over the time from 15.0% (2011) to 30% (2015). As 1st-line treatment, CM was administered in 27% of compared with more than 48% of patients receiving CAPE/VRL-based regimens. Overall Response Rate (ORR) was 28% and Disease Control Rate (DCR) was 79%. Median duration of mCHT was 6.2 months. New generation metronomic regimens produced higher ORR in comparison to old ones (32% vs 13.5%), with similar duration of treatment (6.4 vs 5.4 months, respectively).

Conclusions: The use of mCHT in the treatment of HER2-ve ABC pts has deeply changed across the last 5 years, being new generation regimens used in earlier lines of treatment, producing interesting results in terms of objective response and disease control.

Legal entity responsible for the study: Marina Elena Cazzaniga

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Disclosure: All authors have declared no conflicts of interest.

302P Factors associated with prolonged time to treatment failure with fulvestrant 500 mg in patients with postmenopausal estrogen receptor-positive advanced/metastatic breast cancer (JBCRG-C06; Safari): A subgroup analysis

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Background: This subanalysis of a retrospective, multicenter, cohort study of fulvestrant 500 mg (F500) in advanced/metastatic breast cancer (AMBC) patients in Japan (UMIN000015168) sought to identify clinical factors associated with prolonged time to treatment failure (TTF).

Methods: We analyzed ER+/human epidermal growth factor receptor 2 (HER2)-negative and ER+/HER2-positive patients who received F500 as 2nd- or later-line treatment. Factors investigated were age (≥65/≤65 years), treatment line (≥4th/3rd/2nd), time from AMBC diagnosis to F500 use (<3/≥3 years), prior palliative chemotherapy (no/yes), nuclear or histological grade (1/2/3), visceral metastasis (no/yes), ER expression (+/−), and progesterone receptor expression (+/−). TTF was determined using Kaplan–Meier analysis. TTF data were analyzed using univariate and multivariate analyses with a Cox proportional hazards model.

Results: We registered 1072 patients who received F500 between November 2011 and December 2014 at 16 sites in Japan. In the ER+/HER2− group (n = 828), median TTF was 5.4 months. By univariate analysis, higher age, earlier F500 use and no prior chemotherapy were associated with significantly longer TTF. By multivariate analysis, higher age, longer time from AMBC diagnosis to F500 use, no prior palliative chemotherapy and F500 treatment line were correlated with prolonged TTF (Table). In the ER+/HER2+ group (n = 132), treatment line was correlated with TTF (median 4.6 months) in the univariate analysis ($P = 0.042$); no factors significantly correlated with TTF in the multivariate analysis.

Table: 302P Factors correlated with TTF in ER+/HER2− AMBC patients

ER+/HER2−	Hazard ratio	95% confidence interval	*P*
Age (≥65/<65 years)	0.85	0.73–0.99	0.035
Treatment line (≥4th/3rd/2nd)	1.36	1.22–1.52	<0.001
Time from diagnosis (≥3/<3 years)	0.65	0.54–0.79	<0.001
Prior chemotherapy (yes/no)	1.34	1.13–1.58	<0.001

Conclusions: In ER+/HER2− patients who received F500 as a ≥ 2nd-line treatment, treatment line, advanced age, no prior palliative chemotherapy and a longer time from AMBC diagnosis to F500 use were associated with longer TTF.

Clinical trial identification: UMIN000015168

Legal entity responsible for the study: Japan Breast Cancer Research Group (JBCRG)

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303P Durable complete response in HER2-positive breast cancer: A multicenter retrospective analysis

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Background: Though advanced and metastatic epidermal growth factor receptor 2 (HER2)-positive disease is not curable, a small proportion of patients with HER2-positive metastatic breast cancer remain in prolonged complete remission with anti-HER2 treatment. We hypothesized that some cases of human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer may be curable by trastuzumab. In this large, multicenter retrospective study, we aimed to assess the long-term outcomes for patients with a durable response to trastuzumab.

Methods: We retrospectively evaluated the data of patients diagnosed with HER2-positive metastatic breast cancer who received trastuzumab for more than 2 years as the first-line treatment. Patients diagnosed between April 1, 2001 and December 31, 2014 at 19 institutions in Japan were included in the analysis.

Results: A total of 108 patients were evaluated. Sixteen were met to exclusion criteria. The median follow-up length was 7.7 years. Disease progression occurred in 44/108 (40.7%) patients and 13/108 (12%) patients died. The median progression-free survival was 11.2 years, and as more than 80% of patients were alive 10 years after metastatic breast cancer diagnosis. Of the 108 patients, 57 achieved a clinical complete response. Trastuzumab therapy was interrupted for 27 (47.4%) of these patients (based on the doctor's recommendation for 19 patients, owing to adverse events for 4 patients, owing to unknown reasons for 3 patients, and at the request of 1 patient). Disease progression occurred in 4 of the 27 patients after the interruption of trastuzumab treatment. The median duration of trastuzumab therapy for all 27 patients was 5.1 years (0.9-9.3 years).

Conclusions: In conclusion, we found that some patients showed no evidence of disease after the interruption of trastuzumab therapy. Discontinuation of maintenance trastuzumab in this patient population after a limited time should be explored cautiously while awaiting a global collaborative effort for a randomized trial.

Legal entity responsible for the study: Japan

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304P Characterization of breast cancer responses to metformin

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Background: Over the last six decades, metformin has become one of the most widely prescribed oral medications for type II diabetes. It has recently received considerable attention because of its potential role in reducing the risk of cancer development and its antineoplastic properties. However, the mechanism behind the growth-inhibitory effect of metformin on breast cancer cells remains unclear, with little consensus on which tumour subtypes benefit from treatment. Furthermore, it should be noted that much of the in vitro work published to date has used drug concentrations greatly exceeding the recommended clinical dose, and therefore may not translate directly into clinical practice.

Methods: Non-tumorigenic (MCF10A), pre-malignant (MCF10AT), pre-invasive (DCIS), the three-invasive breast cancer [MCF7, T47D and MDA-MB-231] and the fully bone-homed variant of MDA-MB-231(BM) were treated with metformin and effects on cellular proliferation were evaluated by trypan-blue exclusion and clonogenic assays. The expression levels of metformin transporters mRNA and proteins (OCT1-3, MATE1-2 and PMAT) were evaluated by qRT-PCR, western blot.

Results: The growth-curtailing effect of metformin was achieved at 0.3mM for MDA-MB-231($P = 0.0198$) in cell counting assays. Colony-forming capacity was inhibited in all cell lines tested at 0.03mM, ($P < 0.0001$). The Invasive cancer cells demonstrated strong expression of OCT2, PMAT and MATE1 but minimal positivity for OCT1 and no expression of MATE2. OCT3 is only expressed by the triple negative MDA-MB-231. The mRNA and tissue expression of metformin transporters followed the same pattern.

Conclusions: Clinically relevant doses of metformin inhibited the proliferation and colony formation of different breast cancer subtypes regardless of their receptor status and aggressiveness, including the hard to treat triple negative subtype MDA-MB-231 cells. Expression of various influx and efflux metformin-transporters is essential for cellular response and sensitivity to treatment.

Legal entity responsible for the study: Libyan higher ministry of education

Funding: None

Disclosure: All authors have declared no conflicts of interest.

305P Paclitaxel every-3-weeks versus weekly paclitaxel and versus weekly vinorelbine in metastatic breast cancer

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Background: Single-agent chemotherapy (CT) is widely used in the management of HER2-negative breast cancer patients (pts). As both Paclitaxel (P) and Vinorelbine (V) have demonstrated efficacy in the treatment of Metastatic Breast Cancer (MBC), they are recommended among the standard available CT agents for MBC patients. This study compares the efficacy and safety profile of most frequently used three treatment regimens: Paclitaxel every-3-weeks (3-w-P) versus weekly Paclitaxel(w-P) and versus weekly Vinorelbine (w-V) in MBC. Primary objective: Time to progression (TTP). Secondary objectives: evaluation of safety profiles, clinical benefit and response rate (RR) of all arms.

Methods: In this open-label randomized prospective study, pts were randomized (2:2:1) to receive either: intravenously 3-w-P every 21 days, w-P 80 mg/m^2/week (day 1, 8, 15) every 28 days or w-V 25 mg/m^2/week (day 1, 8, 15) every 28 days. Main eligibility criteria: age $\geq$18 years, documented metastatic disease previously untreated by CT for metastatic setting, ER/PR positive and HER2-negative disease, or triple negative disease. ECOG$\leq$2.

Results: From April 2014 to April 2015, 95 pts were included. 39 received 3-w-P; 38 received w-P and 18 received w-V per protocol. Median age was 58 years (range 38-79), median duration of treatment 11.5 weeks (range 9-24). Efficacy: with a median follow up of 24 months (m), median time to progression (primary endpoint) was 10.3m, 9.8m and 9.6m in 3-w-P arm, w-P and in w-V arm respectively ($p = 0.006$). Safety: w-V was much better tolerated with fewer G 3/4 toxicity events ($n = 2$) than w-P and 3-w-P

(n = 23 and 16). Neuropathy G3/4 was mostly reported in 3-w-P and w-P arm than in V arm (75% vs. 69% vs. 17%). G3/4 alopecia was reported in both P arms (94%) when in V arm G3 alopecia was only in 6% of pts.

Conclusions: Weekly Paclitaxel appeared as effective as every-3-weekly regimen and weekly Vinorelbine, however neurotoxicity is a treatment-limiting toxicity for both Paclitaxel regimen. Vinorelbine had fewer significant grade 3-4 toxicities than both Paclitaxel arms and had better RR. Larger randomised studies are needed to determine the efficacy and overall survival of Paclitaxel versus Vinorelbine.

Legal entity responsible for the study: Lika Katselashvili

Funding: None

Disclosure: All authors have declared no conflicts of interest.

306P All oral combination of vinorelbine and capecitabine as a first line treatment in patients (pts) with metastatic breast cancer (MBC)

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Background: Oral chemotherapy (OCT) represents a step forward in the management of MBC. It has gained an increased importance over the past years. In Egypt, cancer pts living in rural areas are often hours away from the closest treatment center. For these pts, OCT offers a convenient option and seems to be preferred. In first line MBC, oral vinorelbine (OV) with capecitabine (C) is an active full oral combination with response rates (RR) ranging from 48 to 70% in published data. Based on that, we evaluated efficacy and safety of OV-C in first line Her2 negative MBC pts.

Methods: 26 patients were treated. Eligible pts had no previous treatment for their advanced disease. All pts had measurable disease relapsing after (neo) adjuvant AC ± taxane based treatment, WHO PS $\leq$ 2. Pts were treated with OV 60 mg/m^2 D1, D8 for the first cycle and thereafter 80mg/m^2 D1, D8 in combination with (C) 825mg/m^2 twice daily from D1 to D14, every 21 days for 6 cycles. Primary endpoint (EP) was Disease Progression Rate (DPR) (%); secondary EPs were RR, 3 year survival (3YS) and safety.

Results: All 26 pts were included in the analysis. Median age was 53.2 years (range 38.8-77.1); median WHO PS 1 (range 0-2). 58% of the pts were post-menopausal. All pts were treated with AC-based therapy in the (neo)adjuvant setting and 61.5% with an AC+taxane based treatment. 21 (81%) pts had 2 or more metastatic sites; liver (39%), bone (31%) and lung (31%) being the most frequent sites. A median of 4 cycles were given (range: 1-6) with a total number of 102 cycles delivered. ORR was achieved in 14 pts (54%), including 1 complete (4%) and 13 partial responses (50%). In pts who received 6 cycles of treatment, DPR was 40%, while 3 YS was 64.3%. G3-4 neutropenia was noted in 2 (8%) of pts. G3 hand-foot syndrome, nausea-vomiting and neuropathy were seen in 1 (4%), 2 (8%) and 1 (4%) respectively. Dose escalation was possible in 83% of the pts.

Conclusions: In addition to all the benefits of OCT including convenience and prolonged infusion-free survival, our results show that OV-C is also an effective and well tolerated regimen, making it an attractive option for our pts. OCT appears to be a valid alternative to I.V treatment especially for pts and countries where accessibility to treatment centers remains an issue.

Legal entity responsible for the study: Samir Shehata

Funding: None

Disclosure: All authors have declared no conflicts of interest.

307P Retrospective observational study to evaluate the use of halaven plus trastuzumab for the treatment of HER2(+) metastatic breast cancer (MBC) in Spain: HALATRUST study

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Background: Eribulin is a widely used drug for the management of HER2(-) MBC. Given HER2(+) MBC is routinely treated with combinations of anti-HER2 agents plus chemotherapy, frequent use of eribulin in this context has been published in small case series. As today, clinical trial data of eribulin plus trastuzumab comes from phase 2 study in which 1st line patients achieved objective response rates (ORR) of 71% and median progression free survival (PFS) of 12 months, with median overall survival (OS) not yet achieved. HALATRUST is a retrospective, multicentre study designed to evaluate the clinical benefit rate (CBR) and safety profile of this combination in daily clinical practice.

Methods: All known HER2+ MBC patients treated with eribulin plus trastuzumab for a minimum of 1 dose and whose medical records were available and initiated from April 2011 to May 2016 were included. No statistical hypothesis was pre-established.

Results: Of the 48 patients identified in 19 Spanish public and private centres, 47 fully complied with the inclusion criteria and were analysed for efficacy and safety. Relevant baseline characteristics of the population are as follows. Median age: 55 (35 – 86) year-old, women: 45 (96%), positive estrogen and progesterone receptor: 30 (64%) and 19 (40%) respectively, disease burden of $\geq$ 5 lesions: 35 (75%), and median number of previous treatments for MBC: 7. Efficacy and safety results of the study population (n = 47) are summarized in the Table.

Table: 307P

Category	Variable
CBR, n (%)	25 (53.2)
ORR, n (%)	11 (23.4)*
PFS, median (range)	3.6 (3.2 – 4.9)
OS, median (range)	12.1 (9.6 – 19.1)
Dose adjustments, n (%)	9 (19)
TRAE withdrawals, n (%)	3 (6)**

TRAE: treatment related adverse events.
*Including 1 complete response.
**Most TRAE were of hematologic origin.

Conclusions: HALATRUST is, to the best of our knowledge, the largest reported case series on the use of eribulin plus trastuzumab for the treatment of late-line HER2(+) MBC. Results found provide clear evidence on the efficacy and safety of the combination, and highlight the need for its inclusion within the earlier treatment options used in this patient population.

Clinical trial identification: EIS-ERI-2016-01

Legal entity responsible for the study: Eisai Pharmaceuticals Spain

Funding: Eisai Pharmaceuticals Spain

Disclosure: L. Orcajo Rincon, J. Rodríguez-Villanueva: Employee of Eisai Pharmaceuticals. All other authors have declared no conflicts of interest.

308P Lower response to T-DM1 in metastatic breast cancer patients with HER2 IHC score of 2 and FISH positive compared with IHC score of 3

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Background: Ado-trastuzumab emtansine (T-DM1) is the standard second line chemotherapy for HER2 overexpressed metastatic breast cancer (MBC). Tumor HER2 status is measured by either immunohistochemistry (IHC) or fluorescence in situ hybridization (FISH). A previous study showed no difference in objective response rate (ORR) with trastuzumab monotherapy between IHC 3+ and IHC 2+/FISH positive groups. It is not known whether response to T-DM-1 differs between IHC 3+ and IHC 2+/FISH positive patients. The aim of this study is to compare the efficacy of T-DM1 in IHC 3+ group to that of IHC 2+/FISH positive group.

Methods: We retrospectively identified and reviewed the medical records of all patients with HER2 positive MBC who received T-DM1 in our hospital from October 2013 to December 2016. In the efficacy analysis, we excluded five patients who had HER2 negative tumors at metastatic sites.

Results: A total of 44 patients were identified and 36 patients were available for efficacy analysis of ORR. Median age was 58 years old (range 28-80). 95.5% received prior trastuzumab. 45.5% received at least one chemotherapy for MBC, 29.5% received more than four lines of chemotherapy. 79.5% had IHC 3+ and 20.5% had IHC 2+/FISH positive. ORR was 16/30 (53.3%) in IHC 3+ group and was 0/6 (0%) in IHC 2+/FISH positive group (P = 0.024). Median progression free survival (PFS) was 7.0 months (95% CI, 5.58 to 8.42) in IHC 3+ group and was 2.0 months (95% CI, 0.00-4.57) in IHC 2+/FISH positive group.

Conclusions: ORR and PFS were significantly worse in HER2 IHC 2+/FISH positive patients compared with IHC 3+ patients. This is the first report to demonstrate the difference of T-DM1 efficacy by HER2 test results.

Legal entity responsible for the study: St. Luke's International Hospital
Funding: None
Disclosure: All authors have declared no conflicts of interest.

309P Nab-paclitaxel (Nab-P) in HER2-ve advanced breast cancer (ABC) patients (pts): From randomized trials to real-life setting: Results from GIM13 - AMBRA study

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Background: Two randomized studies demonstrated that Nab-P produces a significantly higher overall response rate (ORR), longer Time to Progression (TTP), and greater overall survival (OS) in ABC pts treated with second-line or greater therapy compared with patients who receive conventional Paclitaxel. However, few data are available in the real-life setting, especially for the weekly schedule (wNab-P).

Methods: AMBRA is a longitudinal cohort study, aiming to describe the choice of first and subsequent lines of treatment in HER2-ve ABC pts receiving at least one CHT (SABCS 2016, P5-15-07 & P5-14-09) in the years 2012-2015. For the present analysis, we focused on the use of Nab-P, describing efficacy results according to pts' characteristics.

Results: So far, 791/1500 pts have been registered into the study and 107 (13.5%) received Nab-P in any line of treatment. Median age was 54 years, 88 (82.2%) had Luminal tumours. Twenty-two pts (20.6%) received Nab-P as 1st line, 48 (44.8%) as 2nd-line, the remaining as 3rd-line or greater. Most pts (47.7%) received the every 3 weeks (Q21) schedule, whereas 30 pts (28%) were treated with the weekly (wNab-P) schedule (days 1,8,15 Q28) at different doses: £100 mg/mq: 11 (10.3%), 125 mg/mq,: 15 (14%); 150 mg/mq: 4 (3.7%). The remaining received different schedules or doses. Median number of cycles received was 5 (1-17) and median duration of treatment was 3.5 months in the whole population. No difference has been observed in terms of number of cycles or duration of treatment according to the schedule.

Conclusions: Our results are similar to those obtained in randomized clinical trials and in a recent large real-life study, confirming that Nab-P is currently one of the most promising choice of treatment for ABC pts.

Legal entity responsible for the study: Marina Elena Cazzaniga
Funding: GIM - Gruppo Italiano Mammella
Disclosure: All authors have declared no conflicts of interest.

310P Everolimus-exemestane (EE) vs palbociclib-letrozole (PL) or palbociclib-fulvestrant (PF) in the treatment of metastatic HR+, HER2- breast cancer. An indirect comparison with network meta-analysis

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Background: To compare the efficacy of EE to PF or PL in the treatment of metastatic HR$^+$, HER2$^-$ breast cancer pre-treated or untreated with aromatase-inhibitors (AI) for advanced disease.

Methods: An indirect comparison with a network meta-analysis comparing EE with PL or PF in the treatment of metastatic HR$^+$, HER2$^-$ breast cancer pre-treated or untreated with AI for advanced disease was performed. The Progression-Free-Survival (PFS) was the primary end point of all our indirect comparisons. The indirect comparison was performed both for patients pre-treated with AI and for patients never treated with AI for advanced disease. Efficacy data were expressed as Hazard Ratio (HR) and 95% Confidence Interval (95CI), assuming an α-error of 5% as index of statistical significance.

Results: All the data of the BOLERO-2 trial, the Bachelot et al network meta-analysis (Breast Cancer Treat Rep 2014), the PALOMA-2 and the Paloma-3 trial were analyzed and indirectly compared in a network meta-analysis. 2 orders of comparison were performed: EE vs PL for patients never treated with AI for advanced disease and EE vs PF for patients pre-treated with AI for advanced disease. The pooled HR and 95%CI were respectively 0.597 (0.355-1.005, p = 0.89) and 1.1 (0.7-1.6, p = 0.97) for EE vs PL (never treated with AI) and EE vs PF (pre-treated with AI). No major reasons of clinical and methodological heterogeneity were detected in an independent qualitative analysis, while a moderate quantitative heterogeneity was detected using the I^2 test.

Conclusions: Till today EE and PL or PF represent active treatments for patients with metastatic HR$^+$, HER2$^-$ breast cancer treated or untreated with AI, and no direct comparisons between EE and PL or PF exist in literature. Although our data have not the power to detect any definitive difference in PFS between EE and PL or PF (probably with the exception of EE vs PL, where a trend in favor of EE could bedetected), EE, PL or PF seem to be comparable in terms of PFS; it follows that the better safety or the economic profile could help physicians in daily clinical practice.

Legal entity responsible for the study: Davide Tassinari
Funding: None
Disclosure: All authors have declared no conflicts of interest.

311TiP FRIEND: A randomized pilot study to compare the efficacy and tolerability of fulvestrant 500mg with exemestane as first line endocrine therapy for post-M ER positive HER2 negative ABC patients relapse after adjuvant non-steroidal aromatase inhibitors (NSAI)

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Background: Breast cancer is one of the most common malignancies in women. It has long been acknowledged that oestrogen acts as an endocrine growth factor for hormone-dependent breast cancer. Fulvestrant is a selective estrogen receptor degrader – an ER antagonist with a novel mode of action. Confirm & China Confirm study demonstrated that the efficacy of Fulvestrant 500mg is superior to 250mg. FIRST&FALCON study results confirmed the superior efficacy of fulvestrant over anastrozole in postmenopausal women who have not received prior hormonal therapy. But in the clinical practice, AI are widely used as adjuvant ET for postmenopausal ER+ breast cancer patients. To date there are no randomized trials to compare Fulvestrant 500mg with AI in patients who have relapsed during or after adjuvant non-steroidal AI.

Trial design: The FRIEND trial is a parallel-group, multi-centre study designed to compare the efficacy and tolerability of fulvestrant 500 mg with exemestane 25 mg as first line endocrine therapy in post-M women with ER positive HER2 negative ABC who have relapsed on or after at least 2 years of adjuvant NSAI therapy. Approximately 148 postmenopausal women with ER positive HER2 negative advanced breast cancer who have relapsed whilst on adjuvant NSAI (treatment duration ≥2 years) or after completed adjuvant NSAI treatment will enter this study. Eligible patients will be randomized 1:1 to the following treatment groups: Fulvestrant 500 mg i.m. every 28 (± 3) days plus an additional 500 mg on day 15 (± 3) of first month only; Exemestane 25 mg, orally, once daily. Treatment will continue until disease progression or treatment discontinuation. The primary endpoint is progression-free survival. Secondary endpoints include objective response rate, disease control rate, time to treatment failure, duration of response and overall survival. Efficacy will be determined based on tumor assessments performed by each investigator according to RECIST version 1.1. Safety will be monitored based on the frequency and severity of adverse events (AEs). This study is currently recruiting patients.

Clinical trial identification: NCT02646735
Legal entity responsible for the study: NA
Funding: AstraZeneca China
Disclosure: All authors have declared no conflicts of interest.

312TiP VinoMetro: Phase II study of metronomic daily oral vinorelbine as first-line chemotherapy in advanced/metastatic hormone receptor positive (HR+)/human epidermal growth factor receptor 2 negative (HER2-) breast cancer resistant to endocrine therapy

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Background: Chemotherapy (CTx) is a cornerstone in HR+/HER2- advanced/metastatic breast cancer (a/mBC) after endocrine failure. In this indication, vinorelbine

(VRL) is a well-established cytotoxic drug. There is a high medical need for new options that prolong the time between endocrine failure and intensive CTx, which is commonly associated with impaired quality of life and serious side effects. Metronomic CTx was shown to induce disease control in a/mBC with a favorable safety profile. This innovative approach involving continuous daily dosing of oral VRL, which could provide anti-angiogenic and immune-modulatory properties, has not been investigated so far in this indication.

Trial design: VinoMetro is an open-label, single-arm, phase II study (Simon two-stage minimax) of metronomic daily oral VRL (30 mg/day) as first-line CTx. The study involves strict safety monitoring with an initial safety run-in. It is accompanied by a steering committee and supervised by an independent monitoring board. The main objectives are to estimate efficacy in terms of clinical benefit rate after 24 weeks of treatment (primary endpoint) and the progression-free survival, amongst others, as well as the assessment of safety and quality of life. Patients with HR+/HER2- a/mBC having failed or being no candidate for endocrine therapy (targeted combinations allowed) and being naïve to palliative CTx are eligible, if they exhibit ECOG 0-1. The main exclusion criteria are prior vinca-alkaloids, aggressive disease requiring combination CTx and CNS involvement. Until 2017-04-30, 5 patients were enrolled. It is planned to include 45 (39 evaluable) patients at 8 German sites until 09/2018. Scheduled completion date is 09/2019. Two interim analyses are planned (first analysis: safety evaluation based on the 10 initial patients with predefined stopping rules). VinoMetro is an investigator initiated trial (NCT03007992) sponsored by the University Medical Centre of Johannes Gutenberg-University Mainz, Germany, and supported by an unrestricted grant provided by Pierre Fabre Pharma GmbH (Freiburg, Germany).

Clinical trial identification: EudraCT 2016-000284-17

Legal entity responsible for the study: University Medical Centre of Johannes Gutenberg-University Mainz, Germany

Funding: Pierre Fabre Pharma GmbH, Freiburg, Germany

Disclosure: T. Elger, M. Seehase, L. Schollenberger, C. Ruckes, M. Schmidt: Unrestricted study grant for VinoMetro provided by Pierre Fabre Pharma GmbH (Freiburg, Germany). All other authors have declared no conflicts of interest.

313TiP Open-label phase II study of everolimus plus endocrine therapy in post-menopausal women with ER+, HER2- metastatic breast cancer (Chloe trial)

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Background: BOLERO-2 trial demonstrated that the mTOR inhibitor everolimus was effective in overcoming resistance to endocrine therapy, and BOLERO-4 trial is evaluating the efficacy and safety of combined use of everolimus with letrozole as initial therapy for ER positive HER2 negative metastatic breast cancer (MBC). However, there is no study to evaluate the efficacy of everolimus which can prolong the administration period of aromatase inhibitor (AI) through postponing the acquisition of drug-resistance for MBC with sensitivity to aromatase inhibitor.

Trial design: This study is conducted to examine whether additional administration of everolimus significantly prolongs progression-free survival period in post-menopausal patients with ER-positive HER2-negative MBC which have sensitivity to AI. The inclusion criteria are MBC pts with histologically confirmed ER positive and HER2 negative invasive breast cancer with one or more measurable distant metastatic lesions diagnosed by radiological examination. All patients are receiving AI as the first line hormone therapy for 5-7 months. The pts who are sensitive to AI are randomized to everolimus plus AI arm or the AI alone arm. After randomization, the same AI are continued until progression of diseases and next appropriate regimens are started after that. The primary endpoint is the progression free survival, and the secondary endpoints are overall survival, response rate, disease control rate, adverse events, time to treatment failure and the proportion of patients who continued administration of AI agents for 1 year after the randomized allocation. Sample size for randomized pts was determined to attain at least 80% of power to detect a 5.4 months' difference (10 vs. 15.4 months, HR:0.65) with one-sided alpha of 0.1. Enrollment of 130 pts for randomization is planned over a 2-year accrual period from April 2017.

Clinical trial identification: This trial was registered at UMIN-CTR[umin.ac.jp/ctr/] as UMIN 000025156.

Legal entity responsible for the study: Comprehensive Support Project for Oncological Research of Breast Cancer

Funding: Novartis

Disclosure: T. Toyama: Research funds from Novartis, Kyowa Hakko Kirin, Diichi Sankyo, Ezai, Chugai, Hippon Kayaku and Takeda Co. All other authors have declared no conflicts of interest.

314TiP Selecting patients with oligo-metastatic breast cancer harboring homologous recombination deficiency (HRD) for intensified chemotherapy: The OLIGO-study

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Background: About 5% of patients with metastatic breast cancer (MBC) survive more than 10 years. Long-term survival is mostly seen in patients with limited, maximum of 3-5, distant metastases, often referred to as 'oligo'-MBC. Oligo-metastatic cancer can be treated with curative intent using a multidisciplinary approach that targets the detected metastases, circulating micro-metastases, and any locoregional disease if present. Optimal patient selection is of vital importance.

Intensified chemotherapy in the treatment of breast cancer is controversial, as older studies have not shown a survival benefit in unselected patients. Recent retrospective analyses, however, have suggested that patients with HRD derive significant benefit from intensified chemotherapy compared to conventional chemotherapy.

Trial design: This study will evaluate the difference in event-free survival (EFS) between intensified chemotherapy and conventional chemotherapy as part of a multimodality treatment approach in patients with oligo-MBC harboring HRD. Patients are eligible if they have pathological proven oligo-MBC, defined as 1-3 distant metastases, either as *de novo* or recurrence for which no chemotherapy is given. All lesions must be amenable to surgery or radiotherapy with curative intent. No progression on induction chemotherapy is allowed. Lastly, the tumor has to be HRD by array comparative genomic hybridization. Patients start with 3 cycles of induction chemotherapy, which includes anthracyclines and taxanes in treatment-naïve patients and is adapted according to previously received (neo)adjuvant treatment in others. Patients are 1:1 randomized to another 3 cycles of conventional chemotherapy or 2 cycles of intensified chemotherapy (carboplatin, thiotepa and cyclophosphamide) with stem cell support. Following systemic treatment, all patients receive maximal surgery and/or radiotherapy of locoregional and distant disease. The primary endpoint is EFS at 3 years. Toxicity, time to progression, and overall survival are secondary clinical endpoints. In total 86 patients are required. At the time of abstract submission, 33 patients were randomized.

Clinical trial identification: NCT01646034

Legal entity responsible for the study: The Netherlands Cancer Institute

Funding: Dutch Cancer Society (KWF)

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315TiP AGATA molecular screening program: Implementing precision medicine in patients with advanced breast cancer in Spain

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Background: Metastatic breast cancer continues to be a major cause of cancer death among women globally. In recent years, a better understanding of tumor biology, and the availability of high-throughput technologies has enabled the emergence of precision medicine bringing new expectations and giving rise to molecular screening programs worldwide. Recently, the MOSCATO trial has shown for the very first time that

prospectively sequencing a large panel of genes and utilizing this information to guide treatment choices may improve the outcome of a subset of patients. Some institutions are implementing such strategy as part of the routine treatment decision-making process. However, SOLTI, as a collaborative Spanish network, runs AGATA, the first multi-institutional molecular screening program ever implemented in this country. Patient recruitment started in October 2014 and is expected to conclude in June 2017.

Trial design: Up to 260 patients with metastatic breast cancer will be recruited in 10 participating sites in Spain. Mutation testing is performed prospectively in the genomic laboratories of Vall dHebron Institute of Oncology in Barcelona, 12 de Octubre University Hospital in Madrid, and the University Clinical Hospital of Valencia. Upon molecular characterization and collection of key clinical data, each case is reviewed by a multidisciplinary advisory board, which recommends potential experimental treatments, mainly in the context of clinical trials. During this pilot stage, our primary objective is to determine the success rate in including patients in trials based on their molecular profile. Additional aims are to identify technical and logistical barriers to the implementation of a nationwide program, describe the genomic profiles of the tumors, and assess patient outcomes. Retrospective gene expression (PAM50 + 110 genes and 20 miRNAs) and proteomic analysis (40 markers) will be performed to provide a more comprehensive molecular profile of the tumors that may help explain sensitivity or resistance to administered therapies. Data collected within this program is expected to generate hypotheses for further investigations directed to improve precision medicine.

Clinical trial identification: NCT02445482

Legal entity responsible for the study: SOLTI Breast Cancer Research Group

Funding: Novartis, Mutua Madrileña, Instituto de Salud Carlos III

Disclosure: All authors have declared no conflicts of interest.

316TiP BREAKOUT: A cross-sectional, prospective, observational study of germline BRCA mutation (gBRCAm) prevalence and real-world outcomes among patients (pts) with HER2-negative (HER2-ve) metastatic breast cancer (mBC)

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Background: Several poly (ADP-ribose) polymerase (PARP) inhibitor therapies are currently under investigation to assess their potential for the management of breast cancer. Olaparib (Lynparza) is being evaluated in a Phase III study in HER2-ve mBC pts with a g*BRCA*m (OlympiAD; D0819C00003; NCT02000622). The prevalence of germline and somatic *BRCA* mutations or other somatic homologous recombination repair gene mutations (HRRm) in HER2-ve mBC pts is not well defined. Treatment and clinical outcomes data for pts with HRRm are also limited. The primary objective of this real-world evidence study (NCT03078036) is to estimate g*BRCA*m prevalence in a population of HER2-ve mBC pts not selected by phenotype, age or family history. Treatment patterns and survival outcomes for pts with HRRm will also be examined.

Trial design: BREAKOUT is a prospective, cross-sectional, non-interventional, observational cohort study recruiting HER2-ve mBC pts who have started first-line chemotherapy within 90 days prior to enrollment. If hormone receptor positive, eligible pts will have exhausted all hormone therapy options prior to enrollment and will not have received prior PARP inhibitor treatment. If unavailable from medical records, g*BRCA*m status will be locally determined by blood test and, if negative, archival tumor specimens may be examined with a FoundationOne Dx genomic profile. Pts with a g*BRCA*m, somatic *BRCA* mutation or other HRRm (in *ATM*, *RAD51B*, *RAD51C*, *RAD51D*, *RAD54L*, *BRIP1*, *FANCL*, *PALB2*, *BARD1*, *CHEK1*, *CHEK2*, *CDK12* or *PPP2R2A*) will be followed for ≥18 months to determine the distribution of standard-of-care treatments, progression-free survival (investigator assessed) and overall survival by line of therapy. Approximately 2000 women in 17 countries in North America, the EU and the Asia Pacific region will be enrolled to provide a global g*BRCA*m prevalence estimate with a precision of no more than ±2%. An interim analysis focusing on g*BRCA*m prevalence will be carried out once testing has been completed for all pts. The study is expected to conclude in 2019.

Clinical trial identification: NCT03078036, June 2020

Legal entity responsible for the study: AstraZeneca

Funding: AstraZeneca

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317TiP IMpassion131: Phase III study comparing 1L atezolizumab with paclitaxel vs placebo with paclitaxel in treatment-naive patients with inoperable locally advanced or metastatic triple negative breast cancer (mTNBC)

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Background: Chemotherapy (including paclitaxel [pac]) remains the main 1L treatment for metastatic TNBC but brings limited clinical benefit, highlighting the need for new treatments. Atezolizumab (atezo) blocks the interaction of PD-L1 with receptors PD-1 and B7.1, thus restoring anti-tumor immunity. TNBC is a rational target for atezo due to high PD-L1 expression, elevated T-cell tumor infiltration and high mutational burden. Atezo alone and in combination with nab-pac was well tolerated, with no exacerbation of chemo-associated adverse events, and demonstrated promising clinical activity in mTNBC. Atezo + nab-pac is being further investigated as 1L TNBC treatment in IMpassion130. IMpassion131, a global, multi-center, randomized, double-blind, placebo (pbo)-controlled study, is comparing the efficacy and safety of 1L atezo + pac vs pbo + pac in patients (pts) with untreated, inoperable, locally advanced or metastatic TNBC.

Trial design: Eligible pts are those with inoperable, locally advanced or metastatic TNBC, histologically confirmed; de novo or recurrent disease after early BC chemo treatment completed ≥ 12 mo prior; taxane monotherapy eligible; no prior chemo or targeted systemic therapy for inoperable locally advanced or metastatic disease; ECOG PS 0-1 and measurable disease by RECIST v1.1. Exclusion criteria include known symptomatic CNS disease, prior immunotherapy and history of autoimmune disease. Approximately 495 pts will be randomized 2:1 to receive atezo (840 mg) or pbo (q2w; days 1 and 15 of 28-day cycle) plus pac (90 mg/m^2; days 1, 8, 15 of 28-day cycle) until disease progression. Stratification factors are PD-L1 expression on tumor-infiltrating immune cells (IC; IC0 [< 1%] vs IC1/2/3 [≥ 1%] with VENTANA SP142 IHC assay), prior taxane therapy, presence of liver metastases and geographical region. The primary endpoint is PFS measured by RECIST v1.1. Key secondary endpoints include OS, 12- and 18-month OS rates, 12-month PFS rate, ORR, DOR, and safety. Tumor biopsies will be investigated at baseline, on treatment and at progression to assess biomarkers of response and immune escape.

Clinical trial identification: NCT03125902

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

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319TiP CompLEEment-1: Phase 3b study of ribociclib + letrozole for the treatment of hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2–) advanced breast cancer (ABC) in patients with no prior endocrine therapy (ET) for ABC

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Background: CDK4/6 inhibitor ribociclib was recently approved in the United States in combination with letrozole for the treatment of HR+, HER2– ABC in postmenopausal women with no prior therapy for advanced disease, based on the significantly prolonged PFS versus placebo plus letrozole observed in the pivotal phase 3 MONALEESA-2 trial (Hortobagyi et al. NEJM 2016). The phase 3b CompLEEment-1 study will further evaluate the safety and efficacy of ribociclib plus letrozole as first-line therapy in an expanded patient population.

Trial design: In this open-label study, men or women of any menopausal status with HR+, HER2– ABC will receive ribociclib (600 mg/day, 3 weeks on/1 week off) + letrozole (2.5 mg/day); men and premenopausal women will receive concomitant goserelin (3.6 mg subcutaneous implant every 28 days). Treatment will continue until disease progression or unacceptable toxicity. Patients are limited to $\leq$ 1 line of chemotherapy and no prior ET for advanced disease; patients receiving (neo)adjuvant ET with a non-steroidal aromatase inhibitor must have a disease-free interval of $>$ 12 months. Exclusion criteria include Eastern Cooperative Oncology Group performance status $>$2, or prior CDK4/6 inhibitor treatment. Planned hematologic and chemistry laboratory assessments will be completed every 2 weeks for the first 2 months, then monthly to Cycle 6, and as clinically indicated to Cycle 36. Tumor assessments are recommended every 12 weeks or at intervals per local standard of care during the treatment phase. The primary outcome is safety and tolerability. Secondary outcomes include time to progression, clinical benefit rate, overall response rate, safety, and patient-reported outcomes (PROs). Adverse events and drug-drug interactions will be monitored using CT Scholar; PROs will be collected for female patients using the FACT-B questionnaire to better understand health-related quality of life and treatment side effects. Global recruitment of the planned ~3,000 patients is ongoing, with the majority occurring in Europe.

Clinical trial identification: NCT02941926

Legal entity responsible for the study: Novartis Pharmaceuticals

Funding: Novartis Pharmaceuticals

Disclosure: M. De Laurentiis: Provided consulting or advisory role and participated in a speakers' bureau for Novartis, Roche, Pfizer, AstraZeneca, Celgene and Eisai. M. Martin Jimenez: Consulting or Advisory role from Roche/Genetech, Novartis, Amgen, Pfizer, Lilly. The institution received funding from Novartis. A. Ring: Consulting or advisory role for Novartis, Roche, and Genomic Health. P. Cottu: Consulting or advisory role and received honoraria from Pfizer, AstraZeneca, Novartis and Roche. Conducted research project funded by Novartis, Pfizer and Genotech. K. Zhou, J. Wu, J.P. Zarate: Employee of Novartis Pharmaceuticals Corporation. C. Zamagni: Consulting, advisory role, travel, accomodations, expense and/or research funding from Roche, Genomic Health, Pierre Fabre, Eisai, Novartis, AstraZeneca, Celgene, Medivation, Abbvie, Pfizer, Array BioPharma, Morphotek.

320TiP A phase II trial of mirvetuximab soravtansine in patients with localized triple-negative breast cancer (TNBC) with tumors predicted insensitive to standard neoadjuvant chemotherapy (NACT) including a lead-in cohort to establish activity in patients with metastatic TNBC

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Background: While TNBC patients with pCR/RCB-0 or RCB-1 have excellent survival, those with extensive residual disease (RCB-II or RCB-III) after NACT have poor prognosis. At MD Anderson, through the Moonshot Initiative, we have created a biomarker-driven drug development strategy, ARTEMIS (A Randomized, TNBC Enrolling trial to confirm Molecular profiling Improves Survival) to identify novel targeted therapies for tumors that are predicted to be insensitive to standard NACT. Molecular profiling along with imaging is used to identify patients with chemo-insensitive disease and inform second phase of therapy incorporating targeted agents to improve responses. Folate receptor α (FRα) is a GPI-anchored surface protein encoded by *FOLR1* gene that is overexpressed in multiple cancers including TNBC. Mirvetuximab soravtansine is an antibody-drug conjugate that consists of a monoclonal antibody against FRα conjugated to maytansinoid, a microtubule inhibitor. Nearly 40% of TNBC express high levels of FRα, suggesting that FRα directed therapy is a viable therapeutic strategy.

Trial design: The study will include a lead in cohort (Cohort A) to establish efficacy in metastatic TNBC patients and a neoadjuvant cohort (Cohort B) to determine activity in chemo-insensitive, localized TNBC patients. If $>$ 2 patients in Cohort A have response, the neoadjuvant cohort will be activated. Patients deemed to have chemo-insensitive, FRα+ TNBC identified through the ARTEMIS are eligible for Cohort B. The primary objectives are to determine the response rate of single agent mirvetuximab in metastatic FRa+ TNBC ($>$ 2 lines of therapy) and to determine if mirvetuximab would improve the rates of neoadjuvant pathologic response (pCR or RCB-I) from 5% to 20% in patients with high risk, chemo-insensitive, FRa+ TNBC. A two-stage Gehan-type design with 14 patients in the first stage will be employed for the neoadjuvant cohort (n = 37). Mirvetuximab will be given IV every 21 days (6 mg/kg). Correlatives include assessment of FOLR1/FRα and characterization of biomarkers of immune modulation.

Clinical trial identification: NCT03106077

Legal entity responsible for the study: M.D. Anderson Cancer Center

Funding: NCCN

Disclosure: All authors have declared no conflicts of interest.

321TiP SOLTI-1303 PATRICIA: A phase II study of palbociclib and trastuzumab (with or without letrozole in ER+) in previously trastuzumab-pretreated, postmenopausal patients with HER2-positive metastatic breast cancer

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Background: Despite the high efficacy of anti-HER2 agents, HER2+ metastatic breast cancer remains incurable and in need of additional therapeutic options. Persistent activation of the cyclin D1/CDK4 axis has been identified as a mediator of resistance to anti-HER2 therapy but clinical data of the benefit of CDK4/6 inhibitors in combination with trastuzumab is lacking. PATRICIA is a Simon 2-Stage study to evaluate the efficacy of combining trastuzumab plus palbociclib, with or without letrozole, assessed by progression-free survival (PFS) in pretreated HER2-positive patients.

Trial design: Postmenopausal HER2-positive patients treated with 2-4 prior systemic anticancer treatment lines that must involve trastuzumab or another anti-HER2 treatment in the metastatic setting are included in three cohorts: A: HR-negative, receiving trastuzumab and palbociclib; B1: HR-positive, receiving trastuzumab and palbociclib; B2: HR-positive, receiving trastuzumab, palbociclib and letrozole. Palbociclib is administered at 200 mg/day for 14 days of 21-day cycles. Trastuzumab and letrozole are administered at usual doses. As these combinations have not been tested in phase I trials, we incorporated a 2 cycles-safety run-in phase with the first 6 patients of each regimen. The primary objective is to assess clinical efficacy measured as PFS at 6 months (PFS6). Assuming an increase of at least 20% in PFS6 by the addition of palbociclib +/- letrozole to trastuzumab, PFS6 should be $\geq$ 50% for a cohort to be successful and proceed to stage 2. According to this, it will be necessary to include 15 patients in each cohort in stage 1. In stage 2, each cohort may continue recruitment for up to 46 patients. Translational research searching for predictive biomarkers will be implemented. To date, 43 patients, 13 in A and 15 in each B cohort, have been included in 14 sites across Spain. An independent safety data committee was held twice during the study. The

committee recommended that study continue enrollment as planned. The first stage efficacy analysis is intended for December 2017.

Clinical trial identification: NCT02448420

Legal entity responsible for the study: SOLTI Breast Cancer Research Group

Funding: Pfizer

Disclosure: All authors have declared no conflicts of interest.

322TiP PYTHIA: A phase II study of palbociclib plus fulvestrant for pretreated patients with ER+/HER2- metastatic breast cancer

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Background: Palbociclib is an oral, potent, selective inhibitor of CDK4/6, blocking cell cycle progression from G1 into S phase. Preclinical data indicate that palbociclib has enhanced activity against luminal ER+ human breast cancer (BC) cell lines in vitro, combined with endocrine treatment. Randomized clinical trials showed significant PFS prolongation in patients with newly diagnosed and pretreated metastatic luminal BC, when palbociclib was combined with letrozole and fulvestrant respectively (PALOMA-1/2 and -3 trials). Predictive biomarkers for patient selection to receive palbociclib plus endocrine treatment are still missing.

Trial design: PYTHIA (IBCSG 53-14/BIG 14-04) is a phase II, single-arm, multicenter, study of fulvestrant and palbociclib in postmenopausal women with ER+/HER2-, advanced BC, who progressed after prior endocrine treatment (1st or 2nd line; up to 1 line of prior chemotherapy is allowed). Patients are enrolled concurrently in the AURORA program (NCT02102165), a longitudinal cohort study with extensive molecular characterization of matched primary-metastatic BC, and plasma samples. The primary endpoint is PFS, based on local assessment as per RECIST 1.1. Secondary endpoints are safety and tolerability, as well as disease control rate. Correlative objectives will assess the potential predictive value of: i) mutations and copy number aberrations in a panel of cancer-related genes, ii) gene signatures inferred by RNA sequencing, iii) early FDG-PET/CT assessment performed for a subset of 30 patients, at baseline and Day 28, and iv) a serum thymidine kinase-1 (TK1) assay, performed at baseline, Day 14 and after Cycle 1. The sample size of 120 patients was selected to have 80% power to detect a HR of 2.0 for biomarker-positive patients, with 30-50% prevalence (two-sided $\alpha = 0.05$). Enrollment opened in May 2016, with the target-recruitment being 120 patients at 21 sites in Belgium, Italy and the UK.

Clinical trial identification: NCT02536742

Legal entity responsible for the study: International Breast Cancer Study Group (IBCSG)

Funding: Pfizer

Disclosure: All authors have declared no conflicts of interest.

323TiP EarLEE-1: A phase 3 study of ribociclib + endocrine therapy (ET) for adjuvant treatment of patients (pts) with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2–), high-risk, early breast cancer (EBC)

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Background: Adjuvant ET and chemotherapy reduce the risk for recurrence of HR+, HER2– EBC. However, recurrence is still common in pts with adverse clinical and pathologic features. In the phase 3 clinical trial MONALEESA-2, the cyclin-dependent kinase 4/6 inhibitor ribociclib in combination with letrozole prolonged progression-free survival versus letrozole plus placebo in postmenopausal women with HR+, HER2– advanced breast cancer and no prior therapy for advanced disease (HR = 0.56, 95% CI, 0.43-0.72; $P = 3.29 \times 10^{-6}$; Hortobagyi et al. N Engl J Med. 2016). EarLEE-1 (NCT03078751) investigates the efficacy and safety of ribociclib with ET versus placebo with ET as adjuvant treatment in pts with high-risk EBC.

Trial design: In this double-blind, placebo-controlled, phase 3 trial, ~2000 women and men with fully resected, high-risk, HR+, HER2– EBC (defined as AJCC 8th ed. Prognostic Stage Group III for pts who received adjuvant chemotherapy, or > 2 mm residual disease in axillary lymph nodes and > 10 mm in breast after neoadjuvant chemotherapy) are being randomized 1:1 to ribociclib (600 mg/day, 3 weeks on/1 week off for ~24 months) with ET or placebo with ET. Adjuvant ET may include tamoxifen, letrozole, anastrozole, or exemestane for ≥ 60 months with ovarian suppression for premenopausal women. Randomization is stratified by menopausal status, risk group, and region. Eligible pts must have tumor tissue from the surgical specimen, adequate bone marrow and organ functions, normal serum electrolytes, QTc interval < 450 msec, and completed and recovered from acute toxicities of adjuvant radiotherapy and (neo)adjuvant chemotherapy. The primary endpoint is invasive disease-free survival. Secondary endpoints include recurrence-free survival, distant disease-free survival, overall survival, quality of life, and safety. Global recruitment is ongoing.

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Legal entity responsible for the study: Novartis Pharmaceuticals

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324TiP PATINA: A randomized open label phase III trial to evaluate the efficacy and safety of palbociclib + anti HER2 therapy + endocrine therapy vs anti HER2 therapy + endocrine therapy after induction treatment for hormone receptor positive, HER2-positive metastatic breast cancer

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Background: Pre-clinical data and initial results from clinical studies point to the added benefit of CDK4/6 inhibition when combined with anti-HER2 tx. The current study is designed to evaluate the added benefit of Palbociclib when given in combination with anti-HER2 and endocrine tx maintenance in the 1st line setting of metastatic HER2+HR+ breast cancer.

Trial design: PATINA is an international, open-label, pivotal Phase III study. Primary objective is to demonstrate that the combination of Palbociclib with anti-HER2 plus endocrine tx is superior to anti-HER2 plus endocrine tx in prolonging PFS. Sample size is 496 pts. The study starts after completion of 6-8 cycles of chemotherapy-containing anti-HER2 tx for metastatic breast cancer in the 1st line setting. Pts are eligible provided they are without evidence of disease progression by local assessment (i.e. CR, PR or SD). To account for the need for less intense tx regimens for a subset of pts diagnosed with HER2+ER+ disease, clinicians may recommend the combination of trastuzumab with either a taxane or vinorelbine prior to study initiation. Clinicians might also choose a non-Pertuzumab option for pts previously treated with pertuzumab in the neo(adjuvant) setting. Secondary objectives include measures of tumor control (OR, CBR, DOR), OS, safety and QOL. The translational science main objective is to compare PFS estimates according to *PIK3CA* mutation status assessed by cfDNA analysis. Endocrine tx options are AI or fulvestrant. Premenopausal pts must receive ovarian suppression. The study has a 90% power to detect a hazard ratio of 0.667 in favor of the palbociclib arm. Pts approached to participate in AFT-38 will be asked to indicate on the informed consent forms whether remaining biospecimens and clinical data from the control arm of the study can be shared with the Mastering Breast Cancer (MBC) Initiative. The overarching purpose of the MBC is to create a mechanism for understanding the natural history of metastatic breast cancer by cataloguing longitudinally studied tumor-specific markers and treatment effects.

Clinical trial identification: NCT02947685

Legal entity responsible for the study: Alliance Foundation Trials

Funding: Pfizer

Disclosure: C. Huang: Employee Pfizer Inc. M. Khoeler: Employee and shareholder Pfizer Inc. All other authors have declared no conflicts of interest.

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CNS TUMOURS

3250 Nivolumab (nivo) in combination with radiotherapy (RT) ± temozolomide (TMZ): Updated safety results from CheckMate 143 in pts with methylated or unmethylated newly diagnosed glioblastoma (GBM)

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Background: Prognosis is poor for pts with GBM, as nearly all have recurrence after standard-of-care therapy. Nivo, a fully human IgG4 mAb inhibitor of the programmed death-1 receptor, is approved for the treatment of multiple cancers. Exploratory cohorts 1c and 1d of CheckMate 143 (NCT02017717) assessed the safety/tolerability of nivo in combination with RT ± TMZ in pts with newly diagnosed GBM.

Methods: In cohort 1c, pts received nivo 3 mg/kg Q2W + standard RT + concurrent TMZ (75 mg/m^2 daily) followed by adjuvant TMZ (150-200 mg/m^2; 5 days/28-day cycle for ≥ 6 cycles). In cohort 1d, pts received nivo 3 mg/kg Q2W + standard RT without TMZ. All pts continued to receive nivo until confirmed progression/unacceptable toxicity. Pts (n = 58) were initially assigned to 1c or 1d based on MGMT methylation status (1c, methylated or unmethylated; 1d, unmethylated). Following the initial evaluation, a second group of 55 pts with unmethylated MGMT were randomized 1:1 to 1c or 1d. Pooled safety data for all 113 pts are described here.

Results: Twelve pts with methylated and 43 pts with unmethylated MGMT were treated in 1c, and 58 pts with unmethylated MGMT were treated in 1d. Pts discontinued treatment in 1c (67% each arm) and 1d (83%) mostly due to radiographic progression (1c, 50% [methylated], 37% [unmethylated]; 1d, 64%), study drug toxicity (8%, 9%; 10%), or pt decision (8%, 14%; 0%). AEs (all cause) are summarized in Table. The most common (≥ 30% of pts in any arm) neurological AEs were headache (42%, 47%; 41%) and seizure (25%, 16%; 31%). No deaths due to study drug toxicity were reported.

Conclusions: Nivo with RT ± TMZ was well tolerated, with the frequency of neurological AEs consistent with that in other reports in this disease. These data support continued development of nivo + RT ± TMZ in newly diagnosed GBM in the ongoing CheckMate 498 (NCT02617589) and CheckMate 548 (NCT02667587) trials.

Clinical trial identification: CA209143; Revised Protocol 04d, dated September 15, 2016

Legal entity responsible for the study: Bristol-Myers Squibb

Funding: Bristol-Myers Squibb

Disclosure: G. Vlahovic: Ad Board: Bristol-Myers Squibb, Genentech, Merck. A. Omuro: Ad Board: Bristol-Myers Squibb, AstraZeneca, Merck, Alexion Therapeutics & Juno Therapeutics. Consulting: Stemline. D.A. Reardon: Honoraria, & Consulting: Abbvie, Amgen, Bristol-Myers Squibb, Genentech/Roche, Merck, Juno. Speakers Bureau: Genetech/Roche, Merck. Research funding: Celldex, Incyte, Inovio, Midatech. M. Lim: Honoraria & Consulting: Bristol-Myers Squibb, Merck, Agenus, Oncours. Research funding: Bristol-Myers Squibb, Agenus, Accuray. Patents/Royalty: John Hopkins. S. Sahebjam: Consulting: Bristol-Myers Squibb, Merck. Research funding: Bristol-Myers Squibb, Cortice, Merck. T. Cloughesy: Consulting: Bristol-Myers Squibb, Pfizer, Tocagen, Roche, Novocure, Nektar, VBL, Abbvie, Upshire Smith, Notable Labs, Oxigene, NewGen, Agios, Cortice, MedQia, ProNai, Wellcome, Merck, Insys, Human Longevity, Sunovion, Boston Biomedical, Alexion, Novogen. V. Potter, P. Paliwal, M. Carleton: Employee of Bristol-Myers Squibb. R. Zwirtes: Employment & stock holder with Bristol-Myers Squibb. J. Sampson: Royalties: Celldex. Shares/Equity: Istari Oncology. Consulting: Bristol-Myers Squibb. A.A. Brandes: Travel grant to ASCO by Roche. All other authors have declared no conflicts of interest.

Table: 3250 Summary of AEs (all cause)

Pts, n (%)	1c: Nivolumab + RT + TMZ		1d: Nivolumab + RT
	Methylated *MGMT* n = 12	Unmethylated *MGMT* n = 43	Unmethylated *MGMT* n = 58
AEs in ≥ 30% of pts in any arm			
Fatigue	9 (75)	22 (51)	25 (43)
Headache	5 (42)	20 (47)	24 (41)
Nausea	6 (50)	13 (30)	10 (17)
Seizure	3 (25)	7 (16)	18 (31)
Constipation	2 (17)	14 (33)	4 (7)
Alopecia	4 (33)	4 (9)	7 (12)
Other neurological AEs in ≥ 15% of pts in any arm			
Cognitive disorder	2 (17)	3 (7)	6 (10)
Dizziness	2 (17)	4 (9)	5 (9)
Visual field defect	2 (17)	2 (5)	1 (2)
Immune-mediated AEs in > 2 pts in any arm			
ALT increased	3 (25)	8 (19)	7 (12)
Rash	1 (8)	7 (16)	9 (16)
AST increased	3 (25)	7 (16)	5 (9)
Diarrhea	0	6 (14)	8 (14)
Hypothyroidism	1 (8)	4 (9)	6 (10)
Rash maculopapular	3 (25)	2 (5)	4 (7)
Bilirubin increased	1 (8)	1 (2)	3 (5)
Creatinine increased	0	3 (7)	2 (3)
Grade 3/4 AEs in > 2 pts in any arm			
Lymphocytes decreased	2 (17)	5 (12)	2 (3)
Lipase increased	0	3 (7)	4 (7)
ALT increased	1 (8)	2 (5)	3 (5)
Seizure	1 (8)	3 (7)	2 (3)
Tumor flare	0	1 (2)	4 (7)
Hyponatremia	1 (8)	0	3 (5)
Muscular weakness	0	1 (2)	3 (5)
Serious AEs in > 2 pts in any arm			
Seizure	3 (25)	4 (9)	7 (12)
Malignant neoplasm progression	2 (17)	2 (5)	3 (5)
Pyrexia	1 (8)	3 (7)	2 (3)
Tumor flare	0	2 (5)	4 (7)
Headache	0	4 (9)	1 (2)

326O The association of programmed death-ligand 1 (PD-L1), programmed cell death (PD-1), tumor infiltrating lymphocytes(TILs) and isocitrate dehydrogenase (IDH-1) mutation in glioblastome multiforme(GBM)

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Background: PD-L1, PD-1 expression, TILs and IDH-1 mutation associations and their prognostic importance in GBM are planned to assessed in the study.

Methods: GBM patients who were newly diagnosed and operated between February 2006 to February 2017 were included retrospectively in the study. In initial tumor specimens PD-L1, PD-1 expression, CD4(+) ve CD8(+)TILs, IDH-1 mutation were assessed. For IDH-1 mutation analysis real time PCR tecnique was used, for PD-L1 and PD-1assessment immunohistochemistry was performed by Ventana® antibody (clon-SP263, ROCHE). For PD-1, PD-L1, CD4, CD8 TILs intensity was graded as low, moderate, dense and estimated in percents. The cut off value assumed as $\geq$ 5% for PD-L1, PD-1 positivity. Kaplan Meier, Cox regression tests and SPSS 23 were used.

Results: Ninety patients were included. The mean age was 57$\pm$ 12,3 and 57 (63,3%) patients were male. Fourty eight (53,3%) patients were received chemoradiotherapy and chemotherapy with temozolamide after operation. Two different staining patterns were diagnosed for PD-L1 expression as diffuse fibrillary [29 (32,2%)] and membranous staining [15(16,7%)]. Thirty (33%) patients have IDH-1 mutation. TILs were seen intensely in the perivascular field, which is rarely found in the intratumoral area and in that TILs, PD-1 staining grade was dense. We also observed a positive correlation between the density of TILs in the intratumoral/perivascular fields and the percentages of PD-L1 positivity. ($p < 0{,}0001$, $r = 0{,}46$). The intensity of both TILs in perivascular areas were significantly lower in PD-L1 (-) tumors than in PD-L1 (+) tumors ($p < 0{,}001$). No association was found between IDH-1, PD-L1 and TILs. We didn't find any significant effect of age, sex, PD-L1 positivity and IDH-1 mutation status on survival. (log rank 0,03;0,78; 0,13; 0,64 respectively.) Presence of dense intratumoral PD-1 (+)TILs and dense membranous PD-L1 staining were found as positive; advanced age was found as negative independent prognostic factors by multivariate analysis.

Conclusions: Staining pattern of PD-L1 and the density of PD-1 positivity in TILs may be a prognostic importance in GBM.

Legal entity responsible for the study: Didem Şener Dede

Funding: None

Disclosure: All authors have declared no conflicts of interest.

327O Epidermal growth factor receptor (EGFR) amplification rates observed in screening patients for randomized clinical trials in glioblastoma

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Background: EGFR is a key oncogenic target for the treatment of glioblastoma. EGFR amplification is detected in ~50% of tumors. Depatuxizumab mafodotin (depatux-m), formerly called ABT-414, is a tumor-specific antibody-drug conjugate that preferentially targets tumors with EGFR amplification. Herein, we report the frequency of EGFR amplification in 2 large-scale glioblastoma clinical trials of depatux-m.

Methods: Assays for EGFR abnormalities were performed centrally in 2077 (as of May 1, 2017) glioblastomas during screening for 2 randomized glioblastoma trials with depatux-m: INTELLANCE 1 (NCT02573324) for newly diagnosed patients ($n = 1001$), and INTELLANCE 2 (NCT02343406) for recurrent disease ($n = 1076$). EGFR amplification, required for eligibility in both trials, was determined by fluorescence in situ hybridization and defined as at least 2 copies in at least 15% of cells. EGFRvIII data will be reported at the meeting.

Results: The frequency of EGFR amplification was ~50% (Table), similar to published rates. Higher rates were observed in patients from the Americas/Europe (53–57%) than from Asia (34%).

Table: 327O Pooled Screening Results: INTELLANCE 1 (phase II/III, newly diagnosed) and INTELLANCE 2 (phase II, recurrent)

World Region	Not Amplified	EGFR Amplified	Total Patients	Positive, %
Africa	5	4	9	44.4
Americas	213	238	451	52.8
Asia	132	69	201	34.3
Europe	518	672	1190	56.5
Middle East	19	21	40	52.5
Oceania	106	80	186	43.0
Total	993	1084	2077	52.2

Conclusions: This study represents the first report of lower EGFR amplification rates in patients from Asia with glioblastoma to our knowledge. This observation requires further study.

Clinical trial identification: INTELLANCE 1: NCT02573324 INTELLANCE 2: NCT02343406

Legal entity responsible for the study: AbbVie Inc.

Funding: AbbVie Inc.

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328O Low grade glioma patients with IDH mutation and 1p19q codeletion: What to do after surgery?

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Background: Molecular characterization of low grade gliomas (LGG) is essential for diagnosis and treatment of these diseases. LGG patients (pts) with IDH mutation and 1p19q codeletion (codel) are characterized by a median OS (mOS) longer than 10 years. Thus, the role of treatments and side effects should be carefully evaluated.

Methods: We evaluated LGG pts from our data warehouse ($n = 679$ pts) who received surgery and had sufficient tissue to assess biomarkers characterization. Pts with gliomatosis were excluded. IDH1/2 assessment was performed on formalin-fixed paraffin-embedded samples by qPCR. In wild type cases we performed NGS. 1p/19 codel analysis was performed by FISH.

Results: 93 consecutive LGG with IDH mutation and codel were included. The median follow up (FU) was 96.1 months. Mean age was 40 yrs (range: 25-66); 8 pts (8.6%) underwent biopsy, 61 pts (65.6%) partial resection, 24 pts (25.8%) complete resection. 84 pts (90.3%) were considered high risk using RTOG criteria (> 40 years and/or incomplete resection). Fifty pts (53.7%) received only FU, 17 pts (18.3%) received chemotherapy (CT), 18 pts (19.4%) received radiotherapy (RT), 8 pts (8.6%) received RT + CT. Median PFS (mPFS) was 59.6 months (95%CI: 41.8-77.4) and was significantly longer in pts who received postsurgical treatments (79.5 months, 95%CI: 66.4-92.7) than pts who received FU (46.3 months, 95%CI: 36.0-56.5; $P = 0.001$). mPFS was 50.8 months (95%CI: 17.4-84.3), 103.6 months (95%CI: 11.7-195.6) and 120.2 months (95%CI: 40.5-199.8) in pts treated with CT alone, RT alone and RT + CT, respectively. Multivariate analysis showed that receiving a post-surgical treatment ($P < 0.001$), and the extent of resection ($P = 0.043$) were significantly correlated with PFS.

Conclusions: Our study evaluated the role of treatments in LGG pts assessed with NGS and FISH. Post-surgical treatments are crucial to extend PFS in pts with IDH mutation and codel. The choice of post-surgical treatments seems to have a role, being CT alone less effective than RT and RT+CT. Longer FU is needed to provide information about OS.

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Funding: None

Disclosure: All authors have declared no conflicts of interest.

329PD Prognostic factors for IDH mutant molecular astrocytomas

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Background: Low grade glioma (LGG) is a heterogeneous disease. Recently, the 2016 WHO classification of brain tumors has underlined the role of genetic and molecular features. Molecular astrocytomas have been defined as grade II tumors with IDH mutation and without 1p19q codeletion.

Methods: We evaluated 213 consecutive patients with LGG who received surgery or biopsy and had adequate tissue to assess molecular characterization. IDH mutations were assessed by immunohystochemistry (IHC) and next generation sequencing (NGS) in IHC negative cases, MGMT methylation status was assessed by polymerase chain reaction (PCR) and 1p19q deletion was assessed by fluorescence in situ hybridation (FISH).

Results: 198 patients (93.0%) showed IDH-mutation. Ninety patients (49.2%) were 1p19q non codeleted (molecular astrocytomas). The median follow up was 98.3 months. Median age was 36 (range: 18-69), 11 patients (12.2%) underwent biopsy, 48 (53.3%) patients subtotal resection and 31 (34.4%) patients total resection. According to RTOG criteria, 68 patients (75.6%) were considered high risk (> 40 years and/or incomplete resection), and 22 patients (24.4%) were considered low risk (< 40 years and/or complete resection). 59 patients (65.5%) did not receive any post-surgical treatment, but only follow-up, 31 patients (34.4%) received post-surgical treatments: 20 (22.2%) received radiotherapy (RT), 7 (7.8%) received chemotherapy (CT), 4 (4.4%) received CT+RT. Median progression-free survival (PFS) was 44.3 months. Significant differences in PFS were observed between treated and untreated patients (64.8 vs 35.7 months $p = 0.004$) and treated with RT versus follow-up (60.0 vs 35.7 months $p = 0.004$). Multivariate analysis confirmed the treatment after surgery as an independent prognostic factor (HR 0.456, $p = 0.005$). Median overall survival (OS) was 164.0 months. At time of analysis no significant differences in OS were available.

Conclusions: Post-surgical treatment after resection of IDH mutant molecular astrocytomas is an independent prognostic factor. A longer follow-up is needed for worthy results in terms of OS.

Legal entity responsible for the study: N/A

Funding: None

Disclosure: All authors have declared no conflicts of interest.

330PD Galectin-1 (Gal-1) expression as a prognostic factor in a homogenous cohort of glioblastoma (GB) (Gliocat study)

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Background: Gal-1 is a β-galactoside binding protein that plays an important role in cancer progression and has been implicated in resistance to chemotherapy and anti-VEGF therapy. Gal-1 mediates glioma aggressiveness and its expression increases with grade and correlates with worse outcome. Our aim was to evaluate the prognostic significance of Gal-1 in a homogenous cohort of GB.

Methods: GLIOCAT is a multicenter study of newly diagnosed 432 GB patients treated with Stupp regimen. Tissue from 272 patients was used to generate a tissue microarray and Gal-1 expression in cytoplasm (C) and nucleus (N) was analyzed by immunohistochemistry. Results were evaluated by three reviewers and quantified by H-Score. Expression levels were correlated with clinical characteristics, known prognostic factors and response to anti-angiogenic treatment. Preliminary results will be presented at 2017 ASCO, abstract e13526. We will report here the final results.

Results: We defined a cut off for Gal-1 H-Score of ≥ 157 (cytoplasm, C) and ≥ 123 (nucleus, N). High combined Gal-1 expression significantly correlated with worse OS. No correlation was found with PFS.

Multivariate analysis: KPS, age, MGMT methylation status, extent of resection and Gal-1 expression were independent prognostic factors for survival. High Gal-1 expression correlated with worse OS at recurrence in 61 patients with antiangiogenic treatment (13.8 vs 17.8months, $p = 0.084$) and in 80 with other therapies (17.7 vs 29.3months, $p = 0.001$).

Table: 330PD

H-Score	n	mOS (months) (range)	p value
Combined H-Score Low (C < 157 and N < 123)	213 59	16.69 (13.98-19.39)	0.008
High (others)		13.76 (9.93-17.56)	

Conclusions: Gal-1 expression represents an independent prognostic factor for GB patients treated initially with standard therapy and with other therapies at recurrence.

Legal entity responsible for the study: Gliocat group

Funding: Marató TV3 2012

Disclosure: All authors have declared no conflicts of interest.

331PD Impact of WHO 2016 update and molecular markers in pleomorphic xanthoastrocytoma

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Background: There is a relative paucity of data regarding outcomes of pleomorphic xanthoastrocytomas (PXA) particularly with respect to the impact of emerging molecular markers. We present our institutional experience of PXA and correlate their outcomes with various clinical and pathological factors.

Methods: Between 2006 to 2016, 37 patients with histologically verified PXA form the study cohort. All patients underwent maximal safe resection; those who had good resection, low MIB-1 index and young age were observed. Adjuvant radiotherapy was given in patients with atypical features on histology, high MIB-1 index and recurrence after first surgery or with significant residual disease. Patients diagnosed with anaplastic PXA were managed by multi-modality approach comprising maximal safe resection, radiotherapy and systemic therapy. BRAFV600E mutation testing was attempted in all 37 paraffin embedded tissue blocks. Progression free survival (PFS) and overall survival (OS) and potential prognostic factors affecting outcomes were analyzed.

Results: Median age at diagnosis was 20 years (range 4–45). Tumors were predominantly in the temporal lobe and seizures were the most frequent symptom at presentation. Gross total resection (GTR) was achieved in 23 cases (62%), a subtotal resection (STR) in 13 cases (35%) and biopsy in one patient. At a median follow-up of 33 months, 3-year and 5-year OS was 80.2% & 74% respectively. Patients who underwent GTR had a better PFS as compared to those who underwent STR (3-year estimates 85.6% vs. 32.3%; $p = 0.001$). 10 patients (27%) were classified as having anaplastic PXA. PFS was significantly superior in PXA grade II as compared to the anaplastic PXA group (3-year estimates 80.2% vs. 32%; $p = 0.007$). Of the 27 patients where BRAF V600E testing was successful, 13 patients showed a mutation (48%). 3-year PFS & OS survival in BRAFV600E mutated patients was 51.9% & 76.9% compared to 73% & 75% in BRAFV600E non-mutated patients, respectively. No patient had an IDH1 mutation.

Conclusions: Anaplastic PXA has worse outcomes as compared to PXA grade II. This data may provide valuable insights and set as a benchmark for imparting targeted therapies.

Legal entity responsible for the study: Nil

Funding: Brain Tumour Foundation of India

Disclosure: All authors have declared no conflicts of interest.

332PD Change of PD-L1 expression status of high grade glial tumors at recurrence and its effect on survival

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Background: Although immunotherapy is not an established treatment option in high grade glial tumors, trials are ongoing. One of the main predictive factor for response to

immune checkpoint inhibitors is PD-L1 expression status and this can change over time with the effect of therapies like chemotherapy and radiotherapy. The aim of this study is to determine whether PD-L1 expression status changes in recurrent gliomas after chemoradiotherapy and the impact of this change on survival.

Methods: PD-L1 expression of 29 patients was evaluated by an expert pathologist with immunohistochemistry. PD-L1 positivity was defined as expression in $\geq$ 1% of tumor cells. Change in PD-L1 expression status was defined as an absolute 5% difference between two resections.

Results: Of the 29 patients, 15 patients (51.7%) had PD-L1 expression in $\geq$ 1% of tumor cells and 7 patients (24.1%) had PD-L1 expression in $\geq$ 10% of tumor cells at diagnosis. Median survival of patients with baseline PD-L1 <%10 was 26 months, and in patients with PD-L1 $\geq$%10 was 18 mo ($P = 0.063$). The PD-L1 status did not change in 17 patients (58.6%). 8 patients had PD-L1 negative tumors both at diagnosis and at recurrence, while 9 patients had PD-L1 positive tumors both at diagnosis and at recurrence. In 6 patients (20.7%) a negative-to-positive switch and in 6 patients (20.7%) a positive to negative switch were seen. The change in PD-L1 status over time was not statistically significant. The change of PD-L1 over time did not influenced overall survival of the patients ($P = 0.45$).

Conclusions: The PD-L1expression status changes in more than 40% of high grade glial tumors at recurrence after receiving chemotherapy and radiotherapy. So immune responsiveness of glial tumors can be modified by treatments. As the patients in this study did not receive immunotherapy after recurrence, the change in PD-L1 expression probably did not affect survival.

Legal entity responsible for the study: Basak Oyan, Seyma Eren, Ozlem Sonmez

Funding: Yeditepe University Hospital

Disclosure: All authors have declared no conflicts of interest.

333PD Meta-analysis of the effect of rituximab in the treatment of primary central nervous system lymphoma

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Background: Primary central nervous system lymphoma (PCNSL) is a rare subtype of agressive non-hodgkin lymphoma (NHL), and is most commonly of B cell phenotype. The standard treatment is not well established but high dose methotraxate is the most commonly used regimen. Intravenous rituximab (iv Rtx) treatment is integrated into the protocols for systemic B cell lymphomas. However there are mixed results with the use of Rtx. The aim of this meta-analysis is to investigate the role of iv Rtx in the treatment of PCNSL.

Methods: PubMed and EBSCOhost databases are searched for rituximab, primary central nervous lymphoma, rituximab, survival. Browsing databases was done in English.

Results: 580 patients were included to meta-analysis. Pooled hazard ratio showed that overall survival is correlated with iv Rtx (HR, 0,498; 95% CI, 0,366 - 0,678; p:<0,001). Pooled hazard ratio was calculated by using fixed effect model. The quality determinations of 7 studies were done by using Newcastle-Ottowa Scale. The studies were counted low quality with the score 1-3, average quality with the score 4-6, high quality with the score7-9. Median score of the studies was calculated as 5.

Conclusions: In this meta-analysis, we showed that the addition of iv Rtx as part of a treatment protocol for PCNSL has a positive impact on survival.

Legal entity responsible for the study: Mustafa Yıldırım

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334PD Tumor Treating Fields (TTFields) – A novel cancer treatment modality: Translating preclinical evidence and engineering into a survival benefit with delayed decline in quality of life

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Background: TTFields is a novel cancer treatment modality using a patient-operated home-use device delivering alternating electrical fields interfering with cell division and selectively disrupting mitosis. Clinical trials are ongoing in various solid tumors and phase 3 trials in glioblastoma (GBM) were recently concluded.

Methods: TTFields were tested in two large phase 3 trials in patients with recurrent (EF-11; $n = 237$) and newly diagnosed GBM (EF-14; $n = 695$). Both trials aimed at improving overall survival (OS) with TTFields and included quality of life (QOL) using the EORTC QLQ C-30 with brain cancer module (BN-20) as a secondary endpoint.

Results: In recurrent GBM, TTFields monotherapy was compared to best physician's choice chemotherapy and failed to demonstrate a superior OS. However, improved response rate (14% vs 9.6%) and a comparable OS (HR 0.86 [CI 0.66–1.12]; $p = 0.27$) suggested clinical activity. The absence of systemic toxicity was favorably noted by many patients. In newly diagnosed GBM, TTFields was added to standard adjuvant TMZ chemotherapy and led to a significant prolongation of OS (HR 0.63 [CI 0.53-0.76]; $p = 0.000059$), without added systemic toxicity. OS was extended in all patient subgroups tested including MGMT unmethylated tumors and elderly GBM. More TTFields patients reported stable or improved scores on global health status, pain, physical functioning and leg weakness (all $p \leq .01$). Deterioration free survival was significantly longer with TTFields for global health, physical and emotional functioning, pain and leg weakness (all $p < .01$). Time to deterioration was shorter for itchy skin and longer for pain (both $p < .001$).

Conclusions: TTFields are an effective treatment for GBM with a novel mechanism of action and unique delivery method. Patients become rapidly independent in handling the device allowing patients to control their treatment at home with stable or improved QOL. The significant survival benefit observed in GBM serves as a proof of principle and establishes this novel modality as a promising anti-cancer therapy in a variety of solid tumors. Due to the lack of overlapping toxicities it can be easily combined with established treatments.

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335PD Early platelet variation during concomitant chemo-radiotherapy predicts adjuvant temozolomide-induced thrombocytopenia in newly-diagnosed glioblastoma

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Background: Although temozolomide (TMZ) was known to induce thrombocytopenia with subsequent cycle delay, dose reduction and early treatment discontinuation in glioblastoma multiforme (GBM), no early predictive test of these side effects has been yet clearly established. In this context, our aim was to identify the best threshold of early platelet variation predicting TMZ-induced thrombocytopenia during the TMZ maintenance phase and to validate it in an independent series of GBM patients.

Methods: It was a retrospective trial including patients suffering from newly diagnosed GBM and treated with TMZ at 75 mg/m2/day concomitant to radiotherapy (RT) followed by TMZ maintenance, according to the Stupp protocol. In a training set, variations of platelet concentrations occurring from the first week to week 6 (ΔW6) were analyzed to identify the most relevant platelet decrease during RT-TMZ associated with at least one clinically relevant TMZ-induced thrombocytopenia ($\leq$100 G/l) in the maintenance phase. An independent validation cohort was used to validate the performance of the ΔW6 threshold.

Results: A total of 147 patients were included: 85 in the training set and 62 in the validation cohort. Twenty seven patients (18%) experienced at least one TMZ-induced thrombocytopenia in the maintenance phase, respectively 14 (16%) and 13 patients (21%) in each cohort; and was the most frequent cause of TMZ schedule changes (49%, 30/61). A platelet decrease at W6 $\geq$35% (ΔW6$\geq$35%) was identified as the best predictive variation of clinically induced thrombocytopenia with an AUC of 0.83, a sensitivity (Se) of 65% and a specificity (Sp) of 96%. In the validation set, a presence of a ΔW6$\geq$35% of platelet variation was associated with: Se 77% [95% CI 66%-87%], Sp 73% [62%-84%], positive predictive value 42% [29%-54%] and negative predictive value 92% [86%-99%].

Conclusions: Our results showed that a platelet decrease at W6 $\geq$35% during the RT-TMZ phase may be an early, widely faisable and costless marker of clinically relevant TMZ-induded thrombocyponia during the TMZ maintenance. Prospective studies are needed to evaluate the usefulness of this test for early TMZ schedule adaptation.

Legal entity responsible for the study: Cancer Center Henri Becquerel

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336PD Treatment of recurrent glioblastoma (GB) after radiotherapy (RT) and temozolomide (TMZ): A retrospective analysis of the GLIOCAT study

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Background: There is no standard treatment in recurrent GB and overall survival (OS) ranges from 3 to 9 months (m). The aim of this study was to identify clinical or biological factors that guide the best therapeutic strategy.

Methods: We identified 397 patients (Pts) from GLIOCAT database (432 patients uniformly treated with Stupp's regimen) who had recurrent GB: 250 Pts received 1 or more active treatment (TT) and 147 Pts didn't. We analysed clinical and molecular characteristics, treatments received, OS and progression-free survival (PFS).

Results: The median TT lines after recurrence was 1 (0-5). At 1st recurrence surgery was performed in 51 (30 alone), RT in 8 and systemic therapy (ST) in 208 Pts (189 without any local TT): Bevazicumab (BV) $\pm$ Irinotecan (IR) 90; clinical trial (CT) 42; TMZ 27; Nitrosoureas (NU) 27]. Pts without any TT were older ($p < 0.001$), had worse KPS ($p < 0.001$), worse Mini-Mental (MM) ($p = 0.003$), more biopsies than resection ($p < 0.001$) and did not complete the 6 cycles of adjuvant TMZ ($p < 0.001$) analyzed by χ^2. In the multivariate analysis the only two variables statistically significant for OS were receiving treatment at progression (OS 2.5m vs 10.6m $p < 0.0001$) and biopsy versus partial or complete resection at diagnosis ($p = 0.005$). Methylated MGMT tumours had a worse OS from the time of relapse, irrespective of the treatment administered ($p = 0.014$). Salvage surgery did not present better OS ($p = 0.69$). 230 Pts had a 2nd recurrence: 128 received a 2nd line TT (surgery 8; RT 5 and ST 114: BV $\pm$ IR 42; NU 31; TMZ 19; CT 11; other 11). 110 Pts had a 3th recurrence: 42 received a 3th line. Pts who received TT had better OS than those who did not receive TT in 2nd ($p < 0.0001$) and in 3th recurrence ($p < 0.0001$) evaluated by Log rank test (Kaplan-Meier). BV was the TT that obtained the highest median PFS in the 1st and 2nd relapse. There were no significant differences in OS between the different TT regimens (median OS from relapse 7.7 m).

Conclusions: Pts who received TT at recurrence offered a better OS in multivariate analysis. Pts undergoing surgery did not present better OS than those who only received ST. MGMT methylation is not a predictor of better OS in recurrence. Pts treated with BV had longer PFS but not OS.

Legal entity responsible for the study: GLIOCAT

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All other authors have declared no conflicts of interest.

337P Molecular subtypes of gliomas defined by gene expression profiling

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Background: Gliomas are the most common primary brain tumors in adults. The heterogeneity of tumors, the lack of reliable criteria for identifying different subtypes make their histopathological diagnosis and their management complex. The molecular classification is one of the most promising approaches to better characterize gliomas. The aim of this study was to characterize molecular markers from the differential transcriptomic analysis of high and low-grade gliomas.

Methods: Tumor samples were obtained from 81 patients diagnosed with gliomas between 1998 and 2013 at Limoges and Montpellier University Hospitals. Transcripts from brain tumor frozen samples were analyzed by Taqman Low Density Array. Cluster and principal component analyses were performed on a list of 96 selected genes belonging to glioma markers, genes coding for neurotrophins and their receptors or involved in different mechanisms such as glycosylation, autophagy, RTK signaling pathways, hypoxia and angiogenesis. Protein expressions from selected genes were achieved by immunohistochemical staining on Tissue MicroArray.

Results: Firstly, variations in gene expression were noted between the primary tumor and its recurrence and between biopsy and resected surgical specimen for a same patient. To have homogeneous series, only 64 primary brain tumors obtained from resected surgical specimens and free from radiotherapy and/or chemotherapy were presented in this work. Brain tumors were diagnosed as grade II oligo-astrocytoma ($n = 9$), grade III oligo-astrocytoma ($n = 10$), grade III astrocytoma ($n = 8$), glioblastoma ($n = 17$), grade II oligodendroglioma ($n = 9$) and grade III oligodendroglioma ($n = 11$). Using the hierarchical cluster method, we identified gene expression patterns specific of low or high grades and a set of genes of interest appeared significantly over-expressed or under-expressed according to tumor grade ($p < 0.05$). Some of them were correlated to prognosis ($p < 0.05$). Immunohistochemistry analysis confirmed the changes of protein expression between low and high grades.

Conclusions: Our results showed that high and low-grade gliomas differ in their gene expression profiles and several genes might act as new biomarkers for differential diagnosis and prognosis in gliomas.

Legal entity responsible for the study: CHU de Limoges - Hôpital Dupuytren

Funding: None

Disclosure: All authors have declared no conflicts of interest.

338P Chitosan-capped gold nanoparticles impair radioresistant glioblastoma stem-like cells

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Background: Glioblastoma is a rapidly lethal cancer with a stringent need for new treatment strategies. In this study, we tested if chitosan-capped gold nanoparticles (Chit-GNPs) may overcome the limitations of drug concentrations by an increased cell internalisation in glioblastoma stem-like cells (GSCs) and if such GNPs could enhance the response to irradiation.

Methods: GSCs lines were isolated from glioblastoma tumor fragments and characterised with stemness and neural markers. Chitosan biopolymer was used as reducing and stabilizing agent to generate Chit-GNPs through an environmentally friendly synthesis procedure. The fabricated Chit-GNPs were characterized by UV-vis-NIR extinction spectroscopy, transmission electron microscopy and zeta potential measurements. GSCs and two normal cell lines were selected for in vitro investigations. The uptake and cytotoxicity of Chit-GNPs were evaluated relatively to that of citrate-capped gold nanospheres (GNPs) of similar size. Cell lines were treated with increasing concentrations of GNPs and Chit-GNPs and then irradiated with hypofractionated radiotherapy (3 consecutive fractions of 1, 2 Gy) and brachytherapy (one single fraction of 1 and 2 Gy). The effect was evaluated through the MTT cell viability test and confirmed with Trypan blue-based counting.

Results: GSCs proved to express stem-cell markers and were highly resistant to radiotherapy. Their cell viability and proliferation were impaired by chit-GNPs with an IC50 of 10ug/mL, while remaining unaffected by simple GNP used in similar concentrations. Chit-GNPs were 15 nm in size, with a positive zeta potential and proved a superior cell internalisation compared to simple GNPs. Normal cell lines remained unaffected by GNPs and Chit-GNPs. Radiotherapy at the tested doses failed to give an additional anti-cancer effect when combined with GNP treatment.

Conclusions: The enhanced internalisation within GSCs and the cytotoxic effect of Chit-GNPs make this compound a suitable backbone for drug delivery in glioblastoma treatment, particularly as it proved a selective toxicity for cancer cells. Surprisingly, Chit-GNPs were highly cytotoxic to glioma cell lines irrespective of irradiation.

Legal entity responsible for the study: Iuliu Hatieganu University of Medicine and Pharmacy

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Disclosure: All authors have declared no conflicts of interest.

339P Hypoxia, Inflammation and redox status as determinants of malignant progression of cancer stem cells

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Background: Transformed cells live in a hostile environment characterized by lack of oxygen. Hypoxia produces: necrosis with alarmins release; activation of HIF1a. Recent studies have shown that HIF1a controls also the expression of membrane receptors in tumor cells. These receptors are part of the inflammatory reparative response (IRR) and have the capacity to bind and be activated by alarmins. Once activated, their signaling cascades lead to NFkB. Human tumor tissues posses 1-2% of cancer stem cells (CSCs) responsible for the metastatic potential of tumors. In particular, we investigated the overall hypothesis that, in CSCs from a primary tumor, hypoxia links the expression of IRR genes to tumor progression.

Methods: Hypoxia was achieved in a hypoxic chamber, where a 1% oxygen mix was flushed in for 4 min. Hypoxic response as well as efficacy of drugs treatments on CSCs was determined by measuring HIF1a, VEGF and other markers by WB and Immunofluorescence. Inflammation-like status was reproduced by treatment with necrotic extracts. Redox status was determined by the DCFH-DA. Expression of IRR and adhesion genes was determined by RT-PCR.

Results: Initially, two cell lines of Glioblastoma CSCs from two different tumors were selected and the protein and gene expression were analyzed by WB and RT-PCR. WB analysis showed that hypoxia promotes the expression of HIF1a and change the expression of other proteins directly related to HIF1a. Moreover the gene expression by RT-PCR showed many differences among the analyzed markers. Then we used multiple concentrations of digoxin and acriflavine in the two selected cell lines and also necrotic extracts. Both the drugs promote the reduction of the expression of HIF1a and other related markers. Moreover we used the drugs and an invasion assay kit for evaluation of invasive tumor cells. Also in this case, we observed modification in the invasiveness of CSCs.

Conclusions: Hypoxia promotes cells adaptation trough the expression of HIF1a, without new genetic mutations, and modify other HIF-target proteins such as VEGF, HKII, Rage. Using different concentrations of digoxin and acriflavine it is possible to modify protein and gene expression of HIF1a and related markers, modifing the production of ROS and the invasiveness of CSCs.

Legal entity responsible for the study: Casa di cura San Raffaele Pisana - Rome

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Disclosure: All authors have declared no conflicts of interest.

340P The prognostic role of high mobility group box protein-1 in glioblastoma and its relationship with the inflammatory response

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Background: In this study, the prognostic role of HMGB expression determined with immunohistochemistry in patients with glioblastoma, and the relationship with the systemic inflammatory response indicators, NLR and PLR are studied.

Methods: This study included 30 patients who had a histopathologic diagnosis of glioblastoma and 14 patients who underwent surgery for a non-tumoural intracranial pathology in Antalya Education and Research Hospital between 2008-2012. HMGB1 expression was examined via immunohistochemical method.

Results: There were a significant difference of HMGB1 expression between the study and the control group ($p = 0.002$). HMGB1 expression was found positive in 23 patients (76.7%) and negative in 7 (23.3%) patients in the study group. In the control group, it was positive in 4 (28.6%) patients and negative in 10 (71.4%) patients. When NLR was used as the SIR indicator, it was determined as positive in 11 (36.7%) patients and as negative in 19 (63.3%) patients. When PLR was used as the SIR indicator, it was determined as positive in 10 (33.3%) patients and negative in 20 (66.7%) patients. Median follow up period of patients was 7.8 ± 7.2 (Range 0.7-26.1). Median survival of the study group was 9.6 ± 1.8 (95% Confidence Interval Range 6-13.2) (Figure 1). There wasn't any significant difference between HMGB1 expression and survival ($p = 0.692$) (Figure 2). When NLR or PLR was used as the SIR indicator, there wasn't any relation or difference determined between SIR and survival ($p = 0.692$, $p = 0.740$). A significant relation was determined between HMBG1 expression and NLR ($p = 0.29$). NLR was negative in 17 (73.9%) patients with positive HMGB1 expression, whereas it was negative in 2 (28.6%) patients with negative HMGB1 expression. HMGB1 expression suppresses SIR response. There wasn't any relationship between HMGB1 expression and PLR ($p = 0{,}127$).

Conclusions: Results we achieved in our study lead to the opinion that HMGB1 overexpression might have a role in the immune response to the developing tumour in patients with glioblastoma. While treatment strategies are developing in patients with glioblastoma, we believe that HMGB1 could be an important treatment goal.

Legal entity responsible for the study: Mustafa Yıldırım

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341P Impact of hyperbaric oxygenation on the expression of PKD1 protein forms in T98G glioblastoma cell line treated with selected pentabromobenzylisothiourea (ZKK-3)

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Background: Glioblastoma (GBM) is the most malignant brain tumour with poor prognosis and limited therapy effectiveness. Tumour hypoxia is considered as a main reason of GBM's resistance to medical treatment. It seems that improvement of therapeutic response can be achieved by the combination of chemotherapeutics application with refinement of oxygenation status of tumour tissue. One of the novel anti-tumour compounds is isothiourea derivative ZKK-3, which inhibits the activity of protein kinase D1 (PKD1). PKD1 promotes tumour growth and mediates detoxification of mitochondrial reactive oxygen species (ROS). The aim of this study was to examine the impact of hyperbaric oxygenation (HBO) on the expression of PKD1 protein as well as its phosphorylated forms - pPKD1 (Ser 916) and pPKD1 (Ser 744/748) in glioma cells treated with ZKK-3 in vitro.

Methods: Human glioblastoma T98G cell line was cultured in medium supplemented with ZKK-3 and exposed to the various oxygen conditions: normoxia, hypoxia, HBO, double hypoxia, hypoxia/HBO. After 24 hours of incubation cell lysis was made. The level of tested proteins in obtained lysates was examined using Western Blot technique.

Results: Increasing concentration of ZKK-3 caused diminution of PKD1, pPKD1 (Ser 916) and pPKD1 (Ser 744/748) levels in all tested oxygen conditions. Comparison of hypoxia and HBO conditions showed that hyperbaric oxygen administration resulted in enhancement of expressions of all PKD1 forms. Moreover, in groups preincubated in hypoxia conditions the levels of tested proteins were also markedly elevated after hyperbaric oxygenation (hypoxia/HBO) in comparison to the double hypoxia groups.

Conclusions: Increase of PKD1 protein expression as well as its phosphorylated forms evidenced that HBO application resulted in enhancement of oxidative stress in T98G cell line *in vitro*. This combined with ZKK-3 ability to inhibit activities of those kinases gives ground to consider ZKK-3/HBO therapy as a promising therapeutic strategy for patients with malignant gliomas. Acknowledgement: The research was supported by KNOW-MMRC project and Foundation for the Development of Diagnostic and Therapy.

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343P The role of clinical characteristics in low grade gliomas in molecular era

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Background: Low grade gliomas (LGGs) are rare tumors. Molecular characterization has been recently integrated into diagnostic workup of low grade gliomas (LGG) defining specific prognostic features. Moreover, clinical factors, such as age and the extent of resection have a prognostic role in LGG. Here we report a comprehensive analysis on clinical and molecular features impacting on outcome in a large cohort of LGG.

Methods: We evaluated adult LGG patients (pts) which occurred from 1991 to 2015, who received surgery and had sufficient tissue to assess molecular biomarkers characterization. We assessed the status of IDH mutation (using PCR or NGS) 1p19q codeletion (FISH), MGMT methylation (detected with PCR).

Results: 213 consecutive LGG were included. The median age was 38 (range:18–69). Median follow up was 98.3 months, 25 pts (11.7%) underwent biopsy, 124 pts (58.2%) subtotal resection, 64 pts (30%) grosstotal resection. According to RTOG criteria 37pts (17.4%) were low-risk (<40 years with complete resection), and 176 (82.6%) were high-risk. IDH1/2 mutation was found in 93% of pts. 1p/19q codeletion was found in 50.8% of pts, MGMT methylation in 65.3% of pts. Median progression free survival (PFS) was 47.8 months. Median survival was 211.0 months (95%CI: 185.7-236.3) and 164.0 months (95%CI: 123.0-205.0) in low risk and high risk patients patients. Significant factors in univariate analysis are listed in the Table. Multivariate analysis showed that PFS was influenced by extent of resection ($P < 0.001$), IDH mutation ($P < 0.001$) and treatment. IDH mutation ($P < 0.001$) and extent of resection ($P = 0.029$) were significantly correlated with overall survival in multivariate analysis.

Table: 343P

Variable	OS (months)	P	PFS (months)	P
IDH mutation	187.2 vs 32.2	0.001	50.8 vs 16.5	<0.001
1p19q codeletion	189.4 vs 164.0	0.015	57.1 vs 41.1	0.031
MGMT methylation	211.0 vs 148.7	0.013	56.0 vs 44.3	0.024
Surgery (complete vs biopsy)	211.0 vs 83.0	0.038	52.9 vs 40.0	0.011

Conclusions: The definition of LGG outcome is complex. Both clinical and molecular factors are needed to determine prognosis and treatment strategies.

Legal entity responsible for the study: N/A

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Disclosure: All authors have declared no conflicts of interest.

344P IDH wild type low grade gliomas: Who seeks shall find

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Background: The 2016 WHO classification of CNS tumors included molecular parameters in addition to histology to redefine many tumor entities. Low-grade glioma (LGG) are divided into isocitrate dehydrogenase (IDH) wild type or mutant. Absence of IDH mutation is a rare event in LGG, and IDH wild type are considered a provisional entity. The technique used to assess IDH mutation is essential to determine the real impact of this tumor type.

Methods: The observation of a particularly favorable outcome in a group of 42 patients with a diagnosis of IDH wild type LGG (OS = 93.7 months) led us to retest IDH mutation with a more sensitive technique. Next Generation Sequencing (NGS) was used to retest IDH status in tumor samples, the results of NGS assay were compared with previous findings.

Results: Initial assessment of IDH mutation in this 42 patients had been performed using PCR in 19 cases and immunohistochemistry in 2 cases. twenty-one (50%) of the 42 initial IDH wild type LGGs were discovered to be IDH mutant when tested with NGS. Four patients had R132H mutation while in the remaining 17 cases a rare IDH mutation was detected. In particular 4 patients showed IDH2 mutation, 5 patients had IDH1 R132C mutation, 5 patient had IDH1 R132G mutation and 3 patients had IDH1 R132S mutation. Median OS of NGS confirmed IDH mutated LGG was 164.0 months vs 32.2 months for NGS IDH wild type LGG reflecting the very distinct clinical course of these two entities.

Conclusions: Repeating testing in IDH wild type LGG cases is crucial, as well as the technique used to assess this mutation. NGS is able to assess IDH mutations in 50% of patients previously misdiagnosed. IDH wild type LGG remains a rare entity with dismal prognosis.

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Disclosure: All authors have declared no conflicts of interest.

345P Effect of ADM alone or combined with monoclonal anti-programmed death ligand-1 antibody on glioma cell lineU251 and T lymphocytes

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Background: Glioblastoma is the most common primary brain tumor. The current standard therapy for patients with glioblastoma is surgery and combination of radiotherapy with temozolomide chemotherapy. However, the prognosis is still very poor. Much research has been done to improve patient outcomes in glioblastoma. Recently, immunotherapy with immune checkpoint inhibitors, such as ipilimumab, nivolumab, and pembrolizumab shows great clinical improvements in other advanced tumors, which make immunotherapy an attractive strategy in glioblastoma treatment.

Methods: The expression of PD-L1 was determined by flow cytometry. The concentration of adriamycin was determined by CCK-8 assay depending on the inhibition rate of U251 cells, which was set to less then 50%(IC50). After treatment with different concentrations of adriamycin, cell proliferation of T lymphocytes was detected by CCK-8 method, cell apoptosis of T lymphocytes and PD-L1 expression were analyzed by flow cytometry. Treated with different concentrations of adriamycin alone or in combination with PD-L1 inhibitors, U251 cells and T lymphocyte proliferation in co-culture were determined by CCK-8 assay.

Results: The expression of PD-L1 was nearly 70%. The IC50 of adriamycin was 4.298mg/L. Adriamycin could enhance the proliferation of T lymphocytes when concentration was less than 4.298mg/L and could up-regulate the expression of PD-L1. Adriamycin (4.298mg/L) combined with immunotherapy (PD-L1 inhibitor 1.5mg/L) could inhibit glioma cells growth obviously and the number of dead T lymphocytes in co-culture system was reduced.

Conclusions: Adriamycin combined with immunotherapy (PD-L1 inhibitor) is a promising strategy for glioma treatment and our research provides theoretical basis for combination of adriamycin and immunotherapy in glioma treatment.

Legal entity responsible for the study: Shiya Zheng

Funding: Laboratory for Experimental Medicine and Surgery of Southeast University

Disclosure: All authors have declared no conflicts of interest.

346P Prognostic Impact of neutrophil to lymphocyte ratio (NLR) in patients (pts) with recurrent primary malignant brain tumours (PMBT) in phase I (Ph1) trials: The Royal Marsden (RMH) Experience

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Background: The NLR is a marker of systemic inflammatory response and elevated levels have been associated with aggressive disease and poorer outcome in multiple cancers, including prostate, lung and colon cancer. In pts with GBM, elevated NLR prior to any initial therapy is predictive for worse outcomes. For pts with refractory PMBT, the role of NLR is uncertain. We aimed to assess the prognostic impact of NLR, and the impact of corticosteroids (CCS) in pts with PMBT referred for consideration of Ph1 trial.

Methods: Retrospective data were collected on treatment (tx) and tumour characteristics of pts with PMBT referred for consideration of Ph1 trial participation between 06/2004–09/2016. Survival analyses were performed using the Kaplan-Meier method, Cox proportional hazards model; chi-squared test was used to measure associations between categorical variables.

Results: 100pts with advanced, refractory PMBT were referred. All pts had received at least one line of prior tx; median no. of prior systemic therapies was 2; 76% had GBM; 63% required CCS on first assessment. Use of CCS was associated with shorter disease-free survival (HR 1.93, 95% CI 1.21-3.06, $p = 0.005$) and shorter overall survival (OS) in both univariate (HR 2.33, 95% CI 1.44-3.77, $p = 0.001$,) and multivariate analysis [MVA](HR 1.84, 95% CI: 1.05-3.24, $p = 0.034$). Pts with NLR$\geq$4 were more likely to require CCS compared to pts with an NLR$<$4 (81% vs 38%). NLR$\geq$4 was associated with poorer outcomes in all models (OS, MVA: HR 1.73, 95% CI 1.02-2.94, p-value 0.043). Use of CCS did not modify the association between NLR and outcomes. Patients with an NLR$\geq$4 and requiring CCS had the poorest outcome ($p = 0.0364$); median OS(mOS) for pts with NLR$\geq$4 on CCS was 4.1months(m)(SE 0.29, 95% CI 3.29-5.42), vs 19m mOS for pts not taking CCS (SE 8.61 95% CI.36-not reached).

Conclusions: In our advanced PMBT cohort, elevated NLR$\geq$4 remained an independent prognostic indicator for poor outcome, independent of the use of CCS. Pts with elevated NLR requiring CCS demonstrated the worst outcomes – a reminder of the potential relevance of host immunity in PMBT.

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347P Prognostic value of pre-operative neutrophil-to-lymphocyte ratio in patients with glioblastoma multiforme

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Background: Glioblastoma multiforme (GBM) is the most common and aggressive primary brain tumour. GBM development is is closely associated with inflammation status and immune response. The neutrophil-to-lymphocyte ratio (NLR) is a marker of host immune response and its elevation has recently been shown to be a poor prognostic factor in many malignancies including colon, prostate, lung, and bladder cancer. We aimed to investigate the prognostic value of preoperative NLR in GBM patients.

Methods: Between 2010 and 2016; 104 patients had surgery for GBM and were assessed for consideration of adjuvant therapy at our institution. Of these, 80 patients with an evaluable pre-corticosteroid full blood count result were identified and included in the final analysis.

Results: The mean tumor diameter was 41mm, most of them were found in the right hemisphere (56%) and in the temporal lobe (27.5%). 85% of the patients received adjuvant chemoradiotherapy (with temozolamide). Median overall survival was 13.4 moths. Patients with NLR $<$4, had a worse median overall survival at 12.5 months versus 13.8 months in patients with NLR $>$4. But this difference was not statistically significant ($p > 0.05$).

Conclusions: Our results suggest that pretreatment NLR could be a useful marker for predicting prognosis in GBM patients but large scale trials are needed to confirm this.

Legal entity responsible for the study: Ozlem Oltulu

Funding: None

Disclosure: All authors have declared no conflicts of interest.

348P The prognostic role of gender and MGMT methylation status in glioblastoma patients: The female power

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Background: Glioblastoma (GBM) remains an incurable disease. Radiotherapy and temozolomide are the backbone of the treatment. Clinical and molecular factors are essential to define prognosis.

Methods: Data on all new cases of primary brain tumors observed from January 1, 2009, to December 31, 2010, in adults residing within the Emilia-Romagna region were recorded in a prospective registry in the Project of Emilia Romagna on Neuro-Oncology (PERNO). We perform a prospective evaluation about prognostic factors in GBM patients treated with temozolomide concurrent with and adjuvant to radiotherapy.

Results: One hundred sixty-nine GBM patients (median age, 60 years; range 29 – 82) were prospectively evaluated. MGMT methylation status was available in 140 patients. Combining gender and MGMT methylation status we obtained four groups of patients: 36 male pts with methylated MGMT (25.7%), 47 male pts with unmethylated MGMT (33.6%), 32 female pts with methylated MGMT (22.9%), 25 female pts with unmethylated MGMT (17.9%). Results of univariate analysis are summarized in the Table. Overall survival (OS) was significantly different between methylated male and methylated female ($p = 0.028$), methylated male and unmethylated female ($p = 0.031$), unmethylated male and methylated female ($p = 0.002$), methylated female and unmethylated female ($p < 0.001$). In multivariate analysis, gender and MGMT methylation considered together (met female vs met male HR = 0.459; 95% CI 0.242 – 0.827; $p = 0.017$), age (HR 1.025; 95% CI 1.002 – 1.049; $p = 0.032$) and Karnofsky Performance Status (KPS) (HR 0.965; 95% CI 0.948 – 0.982; $p < 0.001$) were significantly correlated with OS.

Table: 348P Results of univariate analysis

	n	mOS	95%CI
methylated male	31	16.3	9.2-23.4
unmethylated male	41	15.6	11.8-19.5
methylated female	26	nr	
unmethylated female	21	17.0	11.8-22.2
total	119	17.0	15.2-18.9

Conclusions: The median overall survival is consistently higher for female pts with methylated MGMT, treated with temozolomide concurrent with and adjuvant to radiotherapy. When considered simultaneously with MGMT methylation status, gender might impact on clinical outcome and should be considered as a prognostic factor.

Legal entity responsible for the study: N/A

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Disclosure: All authors have declared no conflicts of interest.

349P Reduced-intensity bevacizumab in progressive glioblastoma multiforme (GBM) is associated with similar overall survival versus standard-dosing

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Background: Bevacizumab (BEV) has demonstrated activity in glioblastoma multiforme (GBM), particularly with regard to symptom control, however overall survival

(OS) benefits have not been clearly defined in prospective randomised phase III trials. Most studies have used 10mg/Kg q 2wks as standard although some experts suggest a less intensive dose schedule might offer similar benefits at a lower cost and therefore better value.

Methods: We retrospectively analysed data from the prospective database of the national neuro-oncology centre in Ireland. All patients who received BEV at the time of progression for histologically-proven de novo GBM from 2010 to 2016 were included. At our institution there is variable practice between Neuro-Oncologists in terms of BEV dosing schedule - standard BEV dosing (10mg/kg q 2wks or 15mg/kg q 3wks) vs. reduced-intensity BEV (5mg/kg q 2wks or 7.5mg/kg q 3wks). Using the Kaplan-Meier method, we assessed OS in the entire cohort and by BEV dosing schedule.

Results: In total, 118 patients received BEV for progressive GBM. Median OS was 5.6 months for the entire population (range: 0.5-42 months) and OS was 45%, 18% and 2% at 6-, 12- and 24-months, respectively. Patient characteristics by BEV dosing schedule were similar (Table). Median OS was similar in the reduced intensity BEV group (N = 49) at 5.5 months and the standard-dose group (N = 69) at 5.6 months, p=0.55. Quality of life analyses are ongoing.

Table: 349P

	Standard Dose BEV	Reduced Intensity BEV	
	N = 69	**N = 49**	***P*-Value**
Gender	**N (%)**	**N (%)**	
Male	45 (65%)	32 (65%)	0.99
Female	24 (35%)	17 (35%)	
AGE			
< 45 years	10 (14.5%)	8 (16%)	0.92
45-65 years	42 (60.9%)	28 (57%)	
> 65 years	17 (24.6%)	13 (27%)	
MGMT	**Known (50/69)**	**Known (36/49)**	
Methylated	20 (40%)	17 (47%)	0.50
Unmethylated	30 (60%)	19 (53%)	
Time from Diagnosis to BEV start			
< 12 months	36 (52%)	24 (49%)	
12-18 Months	16 (23%)	12 (24%)	0.94
> 18 months	17 (25%)	13 (27%)	
Median Overall Survival post BEV	**5.6 Months**	**5.5 Months**	**0.55**

Conclusions: In this large heterogeneous cohort of patients, OS was similar in patients who received standard or reduced intensity BEV for treatment of progressive GBM. Given the cost of BEV, these results have important implications for value in cancer care.

Legal entity responsible for the study: Cancer Clinical Trials Unit (CCTU), Beaumont Hospital, Dublin, Ireland

Funding: None

Disclosure: All authors have declared no conflicts of interest.

350P An individualized-approach to second-line systemic anti-cancer therapy for glioblastoma

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Background: The optimal second-line systemic anti-cancer therapy (SACT) for recurrent inoperable glioblastoma (GBM) is not known. Generally, patients with a recurrence within 6 months of adjuvant temozolomide (TMZ) are treated with procarbazine/lomustine/vincristine (PCV) regimen and those with a recurrence at least 6 months after completion of TMZ are re-challenged with TMZ (rTMZ). The aim of this study is to evaluate the clinical outcomes of this individualized approach.

Methods: We treated 46 patients with second-line SACT for recurrent GB between 2009 and 2015. The Response Assessment in Neuro-Oncology (RANO) criteria were used to assess treatment response. The Kaplan-Meier method was used to calculate survival. Patient- and disease-related characteristics between the groups were compared using the Fisher exact test.

Results: 31 patients received PCV and 15 patients received rTMZ (Table). The median progression-free (PFS) (3.4 months each) and overall survival (OS) (5.2 months vs. 5.3 months p = 0.482) from the start of second-line SACT were similar for both groups. Compared with the PCV group, the median PFS (19.6 months vs. 8.7 months, p = 0.001) and OS (28 months vs. 13.7 months, p = 0.001) calculated from the date of diagnosis were better for the rTMZ group. Toxicity was acceptable in both treatment groups.

Conclusions: As the individualized approach of second-line SACT in recurrent GB leads to similar survival. Patients who recur more than 6 months after completion of primary chemo-radiotherapy generally have a better survival.

Legal entity responsible for the study: Department of Radiation Oncology, Norfolk & Norwich University NHS Foundation Trust

Funding: None

Disclosure: All authors have declared no conflicts of interest.

351P Levetiracetam offers a survival advantage in patients with epilepsy related to MGMT-unmethylated glioblastoma

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Background: Epilepsy is a common symptom in patients with glioblastoma (Gb). Levetiracetam (LEV), an antiepileptic drug (AED), enhances MGMT inhibition and

Table: 350P

	PCV	TMZ	p value
Median age (years)	57 (range 29-71)	63 (range 34-80)	0.119
Excision			0.613
Debulking	25(80,6%)	13(86,7%)	
Biopsy	6(19,4%)	2(19.4%)	
Radiological Appearacne			0.182
Single	24(77,4%)	14(93.3%)	
Multifocal	7(22.4%)	1(6.7%)	
Adjuvant Treatment			0.816
Radical chemo-RT	25(80.6%)	13(86.7%)	
Radical RT alone	2(6.5%)	1(6.7%)	
Palliative RT	4(12.9%)	1(6.7%)	
Adjuvant treatment completed within 6 months	1 (3%)	11 (73%)	0.001
Median time to progression after ˚rst-line (months)	1.2 (range: 0.7-11.03)	9.8 (range: 1-24.3)	0.001

reduces chemotherapy mediated neuronal toxicity, offering a theoretical benefit over other AEDs.

Methods: 213 Hispanic patients were included. All patients underwent surgery (if feasible) followed by chemoradiation based on temozolomide. Type of AED was selected under treating physician discretion. Recorded variables included demographics, AED, dosage, MGMT status, performance status (PS) and type of surgical intervention. The relationship between overall survival (OS), AED and MGMT methylation status was explored.

Results: Mean age was 53-yo (SD+/-14.7), 56.8% were male, 73% presented with epilepsy after diagnosis and 50.7% harbored methylated MGMT (metMGMT). 41% were treated with LEV, 26% were given another AED and 33% did not require any AED. AED indication was not associated with age ($p = 0.087$), PS ($p = 0.78$) anatomic tumor site ($p = 0.34$) or MGMT status ($p = 0.98$). Median OS was 25.8 months (95%CI 21.6-31.5), 27.9 months (95%CI 23.8-33.7) for those with metMGMT, and 11.83 months (95%CI 7.73-16.67) for non-metMGMT ($p < 0.001$). OS for the group of metMGMT patients treated with LEV was 33 months (95%CI 32.6-33.7) while for the unmethylated population was 36.2 months (95%CI 31.2-37.3; $p = 0.45$). In contrast, OS for patients treated with other AEDs was 25.8 months (95%CI 20.4-31.5) for those who have methylated MGMT and 7.6 months (95%CI 6.53-11.8) for non-methylated ($p < 0.001$). Patients who achieved seizure control and had metMGMT reached an OS of 25.2 months (95%CI 17.5-32.7) compared to 5.3 months (95%CI 4.3-6.2) for non-metMGMT and seizure free patients ($p < 0.001$). By comparing the three treatment groups, LEV in non-metMGMT offered an OS advantage to other AED and non-AED treated patients ($p < 0.001$) whereas this benefit was not observed in metMGMT ($p = 0.639$).

Conclusions: Retrospective analysis of this cohort suggests that LEV modifies OS in non-metMGMT Gb patients making it comparable to those with metMGMT. Further validation of this data in clinical trials is warranted.

Legal entity responsible for the study: Leonardo Rojas

Funding: None

Disclosure: All authors have declared no conflicts of interest.

352P The prognostic role of indicators of systemic inflammatory response in patients with glioblastoma

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Background: High-grade gliomas, among which glioblastomas are the most frequently observed histologic subtype, are the most common primary brain tumors in adults. The standard treatment for glioblastoma consists of maximal safe resection, followed by concomitant chemoradiotherapy. It was reported that inflammatory response plays a major role in malignancy, including tumor progression. This study aimed to determine the prognostic role of the neutrophil to lymphocyte ratio (NLR) and the thrombocyte to lymphocyte ratio (PLR)—both indicators of systemic inflammatory response (SIR)—in patients with glioblastoma.

Methods: This study retrospectively evaluated 90 patients that were treated for glioblastoma.

Results: Median follow-up time was 11.3 months (range: 1-70 months). The 1-year and 2-year overall survival rates were 55.2% and 19.5%, respectively. Univariate analysis showed that there wasn't a correlation between overall survival and gender ($p = 0.184$), comorbid diseases ($p = 0.30$), clinical presentation ($p = 0.884$), or tumor lateralization ($p = 0.159$). The prognostic factors that affected survival—other than SIR—were Eastern Cooperative Oncology Group (ECOG) performance status ($p = 0.003$), and tumor localization ($p = 0.006$). Multivariate analysis showed that overall survival was significantly correlated with SIR based on NLR (HR: 2.41), and ECOG performance status (HR: 1.53).

Conclusions: These findings confirm that the NLR value obtained from peripheral blood prior to treatment can be used as a prognostic factor in patients with glioblastoma. It is known that a high NLR value (NLR ≥ 5) is indicative of aggressive disease with decreased survival; therefore, aggressive treatment modalities can be offered to this selected patient population.

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Disclosure: All authors have declared no conflicts of interest.

353P Which patients with recurrent glioblastoma will require a second surgery during their treatment? A machine learning solution

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Background: Deciding upon the therapeutic approach for patients with recurrent glioblastoma (Gb) is a challenge. Although a second surgery may provide effective palliation, it has yet to be established whether it prolongs survival and/or improves quality of life; previous reported data is scarce to demonstrate that reoperation is indicated for all patients with recurrence. The few studies investigating this issue are retrospective and have been conducted on small series with heterogeneous data sets. The aim of the present study was to analyze potential predictors of outcome in patients with recurrent Gb selected for second surgery.

Methods: A statistical learning model based on artificial neural networks was performed. 144 Hispanic patients with Gb were selected; included variables were age, performance status (PS), MGMT promoter methylation (MGMTmet), IDH1/2, and extent of primary surgical resection (ESR). The objective was to identify patients who were candidates for a second surgery considering multiple variable combination models (342). Based on the overall survival (OS) 17 comparisons were made to identify the best model for later validation.

Results: 41 patients (49.7%) were female, median age was 52-years old (SD+/-14.3), 63 cases (43.8%) were older than 60 years, 125 (86.8%) had a Karnofsky Performance Index (KPS)>80%, 73 (50.7%) had methylated MGMT and 124 (86.1%) underwent total or subtotal primary resection. The best predictive variables for requiring a second surgery were age, PS, extent of surgical resection and MGMT methylation status status. With an area under the curve of 0.984, combined age plus MGMTmet had a sensitivity of 78% and a specificity of 95%. Other models including MGMTmet+IDH, age+ KPS and age+KPS+ESR yielded an AUC of 0.563, 0.861, and 0.854, respectively. All differences were statistically significant with p value <0.05.

Conclusions: The identification of patients who will require a second surgical intervention can be achieved, offering patients and clinicians an objective tool to plan and carry multiple therapeutic options.

Legal entity responsible for the study: A

Funding: None

Disclosure: All authors have declared no conflicts of interest.

354P The prognostic role of age in salvage re-irridiation applied patients with recurrent glioblastoma: A meta-analysis

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Background: Glioblastoma is the most common primary malignant brain tumor in adults. Despite of postoperative adjuvant therapy, glioblastoma recurs in almost all the patients. After recurrence, chemotherapy, carmustine wafer intended for lesions, usage of anti-VEGF, re-operation, re-irradiation are the existent salvage therapy options. In this meta-analysis, the prognostic role of age in Salvage re-irradiation applied patients with recurrence glioblastoma was analyzed.

Methods: PubMed and EBSCOhost databases are searched for malignant glioma, high-grade glioma, recurrence, survival, re-irradiation, re- radiation. Browsing databases was done in English.

Results: 1588 patients were included to meta-analysis. Pooled hazard ratio showed that overall survival is correlated with re-operation (HR,1.042; 95% CI, 1.012-1.073; p:0,006). Pooled hazard ratio was calculated by using fixed effect model. The quality determinations of 4 studies were done by using Newcastle-Ottowa Scale. The studies were counted low quality with the score 1-3, average quality with the score 4-6, high quality with the score7-9. Median score of the studies was calculated as 5.

Conclusions: In this meta-analysis, we showed that for re-irradiation treatment, which is a salvage therapy option for recurrent glioblastoma, the age is an important prognostic factor.

Legal entity responsible for the study: Mustafa Yıldırım

Funding: None

Disclosure: All authors have declared no conflicts of interest.

355P Temozolomide combined with fractionated stereotactic radiotherapy for large brain metastases: A propensity-matched Study

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Background: This study was conducted to investigate the efficacy and safety of temozolomide (TMZ) with fractionated stereotactic radiotherapy (FSRT) for large brain metastases (BMs).

Methods: From 2009 to 2016, 72 patients (pts) with large BMs (diameter>3cm or volume>6cc) undergoing concurrent TMZ and FSRT (Group A, n = 38) or FSRT alone (Group B, n = 34) were compared by using the propensity score matching method at the ratio of 1:1. Finally, 27 pts of each group were matched. FSRT was given by 52-52.5Gy/3.5-4Gy/13-15f, while TMZ was given by 75mg/m^2 concurrently. The disease control rate (DCR, CR+PR+SD) was assessed after 2-3 months from treatment. Toxicity was recorded according to CTCAE, v4.0. Local control (LC), intracranial progression-free survival (IPFS), progression-free survival (PFS) and overall survival (OS) were assessed with Kaplan–Meier method and log-rank test.

Results: The median GTV of Group A and B were 19.7cc (6.02-142.81cc) and 15.7cc (6.27-62.35cc), respectively. During treatment, more lesions in Group A shrank greatly and got re-contoured (39 VS 29, p = 0.005), and the median GTV shrinkage rate was 30.5% versus (VS) 23.1%. After 2-3 months of treatment, the DCR was 97.4% (37/38) in Group A and 85.3% (29/34) in Group B (p = 0.064). The median follow-up time was 20.6 months. Before matching, the LC (p = 0.037) and PFS (p = 0.025) of Group A were significantly greater than Group B. IPFS (p = 0.059) and OS (p = 0.059) were marginally longer in Group A. After matching, the median PFS time and 1-year PFS rate of Group A were significantly greater than Group B (12.7m VS 3.3m and 55.2% VS 26.4%, respectively, p = 0.041). The rate of intracranial progression death of Group A was significantly lower (18.2% VS 45.8%, p = 0.04). Both overall survival time and IPFS were also marginally longer in Group A (MST: 23.7m VS 17.5m, p = 0.064; 1y-IPFS: 61.6% VS 40.7%, p = 0.069), while there was no significant difference in 1-y LC (89.8% VS 84.2%, p = 0.23). There was no severe toxicity in both groups (p = 0.623).

Conclusions: The addition of TMZ to FSRT shows advantages in accelerating the shrinkage of large BMs and might improve intracranial control and overall survival, with no increase of toxicities. Further studies with large sample sizes are warranted.

Clinical trial identification: NCT02654106

Legal entity responsible for the study: Cancer Hospital, Chinese Academy of Medical Sciences

Funding: None

Disclosure: All authors have declared no conflicts of interest.

356P Worsening of quality of life (QoL), cognitive functions (CF) and psychological status (PSY) can predict radiologic progressive disease (RPD) in glioblastoma (GBM) patients (PTS) treated with radiation therapy (RT) and temozolomide (TMZ): A mono-institutional prospective study

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Background: Almost all PTS with GBM treated with RT and TMZ relapse during or after treatment. We performed a prospective study to assess if deterioration of QoL, CF and PSY is a predictor of RPD.

Methods: PTS with newly histologically diagnosed GBM treated with RT and TMZ as first-line therapy and KPS>60 were enrolled. PTS received TMZ for 12 cycles or until unacceptable toxicity or progressive disease. All questionnaires were given to PTS for self-assessment before performing MRI. Macdonald criteria were used for radiological evaluation. We assessed QoL, CF and PSY before starting treatment, at the end of RT, and every 3 months until 9 months after the end of RT using EORTC-C30, BN-20, MMSE and HADS questionnaires. Brain MRI were performed at the same timepoints.

Results: We prospectively enrolled 111 consecutive PTS at our oncological center, Veneto Institute of Oncology, between January 2013 and December 2015. Median age was 59; 69 PTS were male and 36 PTS aged ≥65. PTS showing a RPD reported lower physical functioning (p = 0.018), minor role function (p = 0.0007) and a lower global health status (p = 0.01) than patients without RPD. In addition, they reported greater uncertainty in the future (p = 0.007), increased drowsiness (p = 0.013), increased itchy skin (p = 0.005) and greater weakness in the legs (p = 0.027) compared to PTS without RPD. PTS with RPD were more anxious (p = 0.0021) and depressed (p = 0.0001) than PTS without RPD. The two groups significantly differed in CF (p = 0.0007), especially 1 and 6 months after RT, with worse results in the MMSE for PTS with RPD.

Conclusions: Worsening of QoL, CF and PSY can predict RPD in GBM PTS treated with RT and TMZ.

Legal entity responsible for the study: Veneto Institute of Oncology

Funding: None

Disclosure: All authors have declared no conflicts of interest.

357P Dose distribution after tumor cavity injection in brain glioma patients

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Background: The local delivery of drug into brain has not been widely used because the unpredictable dose distribution and dose-toxicity effects that drug may carry. This study is to investigate the efficacy of drug delivery by intra-cerebral injection.

Methods: 3 patients with deep-seated glioma underwent stereotactic biopsy and Ommaya reservoir implantation. Radioactive agent (^{131}I-chTNT) was injected at a dose of (0.8mCi/cm^3) through Ommaya reservoir. Patients were carefully observed and Post-operational PET was performed to reveal the body distribution of 131I and evaluate the distribution of drugs in whole body.

Results: After the intratumoral injection, most of the drug stayed in the brain tumor and decayed gradually for more than 4 weeks. Although the accumulation of 131I was also found in thyroid and urinary system as well as stomach and large intestine, it disappeared within 2 weeks while strong radioactivity was still seen in the brain tumor.

Conclusions: These images demonstrated excellent localization of the radiolabel in the tumor with little diffusion over time. Intra-tumoral injection of chemical or readioactive drugs is recommendable in the local treatment.

Legal entity responsible for the study: Ming Zhao

Funding: Beijing Capital Developmental Fund (2014-2-5021)

Disclosure: All authors have declared no conflicts of interest.

358P Retrospective analysis to ascertain whether thromboembolic events, patient gender and tumour size have prognostic implications for glioblastoma multiforme

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Background: Glioblastoma multiforme is a rare grade 4 incurable brain malignancy. Well established prognostic indicators for this disease include performance status, age and cognitive function at diagnosis. Presenting with a seizure is also known to predict a better prognosis. Patient gender, tumour size and thromboembolic events have not been previously known to have prognostic significance. The rationale of this study is to identify alternative features which could be used as additional prognostic indicators.

Methods: We conducted a retrospective analysis of all patients diagnosed with glioblastoma multiforme at Derriford Hospital, Plymouth, UK between 2009 and 2016. We analysed factors such as survival time since diagnosis, patient demographics, tumour size at diagnosis, performance status at diagnosis, presenting symptom, treatment undergone and the occurrence of venous thromboembolic events since diagnosis.

Results: 92 patients were included. The occurrence of venous thromboembolism had no impact on survival time (p = 0.386). Male sex appeared to predict a better prognosis than female sex, however, this did not quite achieve statistical significance with a p value of 0.09. Cox regression analysis revealed tumour size on diagnosis to be significantly negatively correlated with survival time, with a p value of 0.012. Our analysis agreed with previous findings that multifocal disease and increased age are poor prognostic indicators, and presenting with seizures is a good prognostic indicator. Patients who underwent radical debulking surgery followed by concomitant chemoradiation had a significantly longer survival time than patients who had best supportive care alone.

Conclusions: Our analysis has shown that increasing tumour size is negatively correlated with survival duration. This link has not been previously established. Female sex may also be a poor prognostic indicator, but our data did not achieve statistical significance so further research investigating this potential link may be warranted. Venous thromboembolic events had no impact on prognosis.

Legal entity responsible for the study: Research Office, Plymouth Hospitals NHS Trust

Funding: None

Disclosure: All authors have declared no conflicts of interest.

359P The standard and high dose chemotherapy dose intensity and their effect on the survival of medulloblastoma using nation-wide treatment protocol

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Background: Medulloblastoma is the most common type of childhood brain tumors. We conducted Korea's nation-wide protocol based treatment for medulloblastoma, and adopted tandem high dose chemotherapy for high risk disease. Here we present the result of treatment in Yonsei Cancer Center using the protocol and elucidate dose-response relationship.

Methods: The patient diagnosed and treated in Yonsei Cancer Center were reviewed retrospectively, from 2006 to 2015. We excluded the patients less than 3 years old and over 30 years old. Dose intensity (DI) was calculated as actual dose level/planned dose level divided by chemotherapy treatment duration. Ind-DI was defined as induction chemotherapy DI and HDCT-DI was as high dose chemotherapy DI. The protocol was composed of 2 cycles of neoadjuvant chemotherapy and 32.4Gy of craniospinal radiotherapy (CSRT) and 50.4 Gy of total tumor dose. After the radiotherapy, 4 cycles of chemotherapy and tandem high dose chemotherapy was done.

Results: Among total 39 patients, 16 were standard risk (SR) and 23 were high risk (HR). The 5 year overall survival (OS) was 92% for SR, and 67% for HR. Disease specific survival (DSS) for HR was 75%, and therefore 8% was treatment related mortality (TRM). The 5Y OS between M0 and M1 status was not statistically different in HR. The ind-DI did not affect in 5Y OS for SR and HR. Ind-DI was strongly correlated with HDCT-DI. The 5Y-OS for HDCT-DI<70% was statistically inferior to HDCT-DI>70%. All TRMs developed in HDCT-DI>90%. Therefore, the reduction of HDCT-DI in the protocol was suggested from this analysis. The responsiveness of induction chemotherapy (complete remission and partial remission) was predictive marker for 5Y-OS ($P = 0.026$). The complete response at the first HDCT was also predictive for 5Y-OS ($P = 0.009$).

Conclusions: The result from the nation-wide protocol was acceptable but high dose intensity was the cause of treatment related mortality. Now the dose of HDCT was reduced to achieve the ideal survival rate from the protocol.

Legal entity responsible for the study: Jung Woo Han

Funding: None

Disclosure: All authors have declared no conflicts of interest.

360P Primary central nervous system germ cell tumours: A single institution retrospective study

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Background: Germ Cell Tumors (GCTs) are 2% of intracranial neoplasms, mainly in the pineal/suprasellar region and in young ages. The overall prognosis, in tumors containing a non-germinomatous component, is poor with a median 5 year overall survival (OS) of under 30%. Treatment recommendations suggest a multimodal approach

Methods: We performed a retrospective review of all consecutive primary intracranial GCT patients (pts) diagnosed and treated at our Institution from 1988 to 2015. Primary aim: to characterize the clinical, demographic and treatment data. Secondary aim: to evaluate overall survival (OS) at 5 and10 years using the Kaplan-Meier method and related prognostic factors

Results: From a total of 45 pts, 30 were males, median age 11 years (P10-90: 5,75–20). The main symptoms were cephalalgia (45%), diabetes insipidus (31%) and vomiting (20%). 53% had endocrinologic disturbances, 44% visual field limitations and 20% pts Parinaud Syndrome. Sixty percent presented with intracranial hypertension. Primary location was the pineal and suprasellar in 56% and 29% of cases. Cranial and Neuroaxial Magnetic Ressonance Imaging (MRI) was the preferred imaging method used in 91 and 53% pts, respectively. The diagnosis was reached by tumour markers in 22,2%, tumour biopsy in 26,6% and surgery in 51,1% pts. Tumour markers were elevated in 69% pts. Fourty-ninve percent of pts had pure germinoma, 15,5% pts had mixed germinoma and 31% pts non-germinoma. Sixty-nine percent of pts underwent intracranial decompression techniques. Sixty-nine percent of pts had chemotherapy regimens (PEI in 18 pts) and 82,2% pts had cranial radiotherapy (with simultaneous neuroaxial irradiation in 17 pts). Complete response was achieved in 91,1% of pts with 22,2% pts recurring. The 5 and 10 OS rate was 88 and 85% respectively (98 and 98% for Germinomas and 82 and 75% for non-germinoma). OS values differences between histologies did not reach statistical significance. In the multivariate analysis only cranial radiotherapy and absence of recurrence were associated with improved survival ($p = 0.003$ and $p = 0.016$, respectively).

Conclusions: First line multimodality treatment achieves good clinical outcomes, with focus on cranial radiotherapy. Disease recurrence is associated with worse outcomes.

Legal entity responsible for the study: Instituto Portugues de Oncologia de Lisboa

Funding: None

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361P Effect of silibinin nutraceutical supplementation in brain metastases of patients with advanced lung cancer

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Background: Silibinin is a bioactive flavonolignan extracted from milk thistle (*Silybum marianum*). We are currently evaluating the pre-clinical activity of silibinin on reactive astrocytes, a major component of the brain metastasis microenvironment shown to play important pro-metastatic functions.

Methods: We present data of patients with lung cancer and brain metastases that have received compassionate use of nutraceutical supplementation with Legasil®, a commercially available silibinin-based nutraceutical, in addition to standard oncologic treatment. We have compared our observed results with the brain GPA index of each patient calculated by Lung-molGPA tool (brain GPA Index).

Results: Eighteen patients have been treated: median age 62 y (range: 35–80); male: 11 (61%); median number of brain metastases: 4 (range: 1-20); median size of the bigger brain metastasis: 26 mm (range: 10-65 mm). Histology: Adenocarcinoma: 14, Large cell: 1, Small cell: 2, Squamous: 1. All patients have received whole brain radiotherapy. Observed overall survival (OS) was significantly superior compared with expected OS calculated by Lung-molGPA (median 22.2 months [95% CI 13.0-32.6] vs 6.9 months [4.2-9.5]; $p = 0.001$). Time to central nervous system treatment failure of silibinin was 26.9 months (95% CI 11.7-42.1 months). Brain tumor progression was observed in 6 patients (33%). Overall response rate at brain disease was 75% (Complete Response:3 patients (20%) and Partial Response: 10 patients (55%)). Only one patient presented brain tumor progression as best response. At data cutoff (May 1st, 2017), 6 (33%) patients remained alive.

Conclusions: These preliminary data suggest that silibinin supplementation contributes to the control of brain metastases in lung cancer patients. Further evaluation of the silibinin use in a phase II clinical trial is warranted.

Legal entity responsible for the study: Joaquim Bosch-Barrera

Funding: None

Disclosure: J. Bosch-Barrera: Research grant of SEOM (Sociedad Española de Oncología Médica, Spain) and an Unrestricted Educational Research grant from Meda Pharma (Germany).

All other authors have declared no conflicts of interest.

362P Melanoma with V600 BRAF mutations and brain metastases: Experience of targeted therapy in a single center

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Background: The effectiveness of chemotherapy (temozolomide, fotemustine, lomustine) alone and in combination with whole brain irradiation in patients with melanoma with cerebral metastases does not exceed 7-10%, without significant impact on overall survival, which is 2-4 months. Targeted therapy has improved the survival of patients with metastatic melanoma with BRAF V600 mutations. In patients with brain metastases targeted therapies allow not only to control systemic tumor process, but also to achieve the effect of treatment of cerebral metastases. So, the efficacy (complete and partial regressions of brain metastases) targeted therapy with BRAF inhibitors vemurafenib or dabrafenib in patients with melanoma with BRAF V600 mutations in metastatic brain lesions, according to the literature, varies from 18.0% to 39.2%, with a median survival of patients from 5,3 to 8,2 months. We evaluated the efficacy of targeted therapy (BRAF inhibitors vemurafenib or dabrafenib as monotherapy and also in combinations with MEK inhibitors cobimetinib or trametinib) in patients with melanoma brain metastases.

Methods: In Russian N.N. Blokhin Cancer Research Center effect of the various schemes targeted therapy were evaluated in 45 patients with melanoma with BRAF V600 mutations and brain metastases. Patients received the following treatment options: dabrafenib (4 patients), dabrafenib + trametinib (11 patients), vemurafenib (25 patients), vemurafenib + cobimetinib (5 patients). Three patients (6,7%) targeted therapy was combined with whole brain irradiation, in eight patients (17,8%) – in combination with stereotactic radiotherapy/radiosurgery.

Results: Complete regression of brain metastases was achieved in 3 patients (6,7%), partial regression in 19 (42,2%), stabilization in 15 (33,3%). Thus, the tumor control in

the brain was observed in 37 patients (82,2%). In 43 patients (95,6%) of 45 were also established metastases in other sites (extracranial lesions). Complete regression of metastases in extracranial lesions was achieved in 1 patient (2,3%), partial regression – in 26 (60,4%), stabilization in 13 (30,2%). The median time to disease progression was 5.5 months. The median survival of patients was 8,5 months.

Conclusions: The data presented indicate that the targeted therapy with BRAF inhibitors as monotherapy and also in combination with MEK inhibitors in patients with metastatic 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.

363P Radioprotective effect of xenon in radiation treatment for brain metastases

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Background: Surgical treatment, whole brain irradiation (WBI) and stereotactic radiation therapy (RT) are the main treatment strategies for solitary brain metastases. Applying additional boost to the bed of removed metastatic foci seems promising for enhancing local control, but increased radiation exposure affects the central regulation and processes that maintain homeostasis. The purpose of the study was to evaluate optimization of adjuvant RT with xenon due to its neurotrophic and neuroprotective effects.

Methods: 16 patients of the control group received WBI with additional boost once a day (60 Gy in 15 fractions), while 12 patients of the main group received similar RT plus inhalations of a xenon/oxygen mixture twice a week. Clinical and neurological examination was performed and the quality of life was assessed (using QLQ-C15 and BN-20 + 2 questionnaires) for all patients during the treatment. Adaptation reactions were identified and the ratio of their anti-stress/stress types (R as/s) was calculated for integral evaluation of the body condition, individual testing tension (Ut) at the Yin Tang point was studied and EEG parameters were analyzed.

Results: Only patients receiving xenon reported reduced rates of headaches and dizziness, disorders of higher nervous activity, reduced degrees of movement disorders; RT course for these patients was performed in compliance with the accompanying therapy. Assessment of the quality of life by the end of the treatment showed significant improvement in such criteria as physical health and loss of appetite, as well as pain relief, in contrast to the control group. Negative dynamics of integral body parameters, R as/s and Ut was lower than in the control group, and some EEG parameters were normalized after xenon therapy.

Conclusions: Xenon therapy is an effective optimization method for radiation treatment of patients with brain metastases. Its radioprotective and stress-limiting effects allow reduction of adverse effects and toxicity and improvement of the quality of life of patients.

Legal entity responsible for the study: Rostov Scientific Research Institute of Oncology, Russia

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Disclosure: All authors have declared no conflicts of interest.

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

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DEVELOPMENTAL THERAPEUTICS

365O Phase 1 safety and clinical activity of BLU-554 in advanced hepatocellular carcinoma (HCC)

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Background: Treatment for advanced HCC remains limited and outcomes are poor. However, emerging data implicate FGF19 as a key HCC driver and suggest its receptor, FGFR4 as a novel therapeutic target. A phase 1 study (NCT02508467) was initiated to assess the safety and clinical activity of BLU-554, a potent, highly-selective oral FGFR4 inhibitor.

Methods: Adult patients (pts) with advanced HCC and well-preserved liver function received BLU-554 once daily on a 4-week cycle following a 3 + 3 escalation/MTD expansion design. Adverse events (AEs) per CTCAE, PK, PD and pathway activation (tumor FGF19 IHC) were assessed. Response was determined by RECIST 1.1 every 8 weeks.

Results: At a 4/20/17 cutoff, 61 pts have been treated with BLU-554 including 25 in dose escalation (140-900 mg) and 36 in the ongoing dose expansion. 48 (79%) pts had metastatic disease, 54 (89%) had failed $\geq$1 prior systemic therapy (48 (79%) sorafenib; 11 (18%) nivolumab) and 29 (48%) had pathway activation (IHC+). Based on safety profile, PK, PD, and anti-tumor activity, 600 mg was the MTD and RP2D. Radiographic tumor reduction and objective response per RECIST 1.1 were observed in IHC+ pts in dose escalation and dose expansion. Of 19 IHC+ pts with $\geq$ 1 radiographic assessment, 11 (58%) pts had tumor reduction: 6 with SD, 4 with PR and 1 with CR (ORR 26%). 6 (32%) IHC+ pts had duration of treatment $\geq$ 6 months. In contrast, only 4 (15%) of 27 IHC negative pts had tumor reduction (all SD) and only 1 (4%) had duration of treatment $\geq$ 6 months. Most AEs (regardless of causality) were Grade (Gr) 1-2, including diarrhea (66%), nausea (43%), vomiting (39%), ALT increase (33%), fatigue, AST increase (29% each), abdominal pain (23%), anemia, and decreased appetite (20% each). AST (13%) and ALT (10%) increase, were the only BLU-554-related Gr 3-4 AEs occurring in $\geq$ 10% of pts. 2 pts experienced DLT (1 Gr 3 abdominal pain; 1 Gr 3 fatigue lasting $>$ 7 days) at 900 mg. 36 (59%) pts have discontinued treatment: 26 disease progression; 5 AE; 3 investigator's decision; 2 withdrew consent.

Conclusions: BLU-554 is well tolerated at the recommended dose of 600 mg and demonstrates important clinical activity in FGF19 IHC+ advanced HCC pts who have failed prior systemic therapy.

Clinical trial identification: NCT02508467

Legal entity responsible for the study: Blueprint Medicines Corporation

Funding: Blueprint Medicines Corporation

Disclosure: D. Sarker: Honoraria: Pfizer, Novartis, Bayer, Ipsen. Advisory board: Blueprint, Baxalta. S.P. Choo: Advisory board +/- honoraria: Norvatis; Celgene; Sirtex, Bristol-Myers Squibb; New Beta-Innovation Oncology; Bio-Cancer Treatment; Research grant: Bristol-Myers Squibb, Sirtex. T. Meyer: Advisory board for Merck, Bristol-Myers Squibb, Bayer and Eisai. Grants from Bayer and BTG. J-H. Yoon: Research grants from Bayer HealthCare Pharmaceuticals, Daewoong Pharmaceuticals, and Bukwang Pharmaceuticals. J-W. Park: Honoraria Support from: Bayer, Merck. Advisory Board of: Bristol-Myers Squibb, Merck. Consulting of: Bristol-Myers Squibb, ONO, Bayer. S. Faivre: Consulting of Bayer, BMS, Lilly, Merck Serono, Novartis. Y-K. Kang: Advisory Board of Blueprint, Novartis, Roche, Merck, Ono, Bristol-Myers Squibb, LSK Biopharma, Daehwa, Taiho. All other authors have declared no conflicts of interest.

366PD Oncolytic herpesvirus therapy for mesothelioma: A phase I/IIa trial of intrapleural administration of HSV1716 (NCT01721018)

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Background: Malignant Pleural Mesothelioma (MPM) remains a major challenge with limited therapeutic options. Disease is frequently confined to the pleura, distant metastases are uncommon and intrapleural treatment is therefore appealing. HSV1716 is a 34.5null oncolytic herpes simplex virus which, in pre-clinical studies, demonstrates cancer cell-specific HSV1716 infection and oncolysis and an anti-tumor immune response. We assessed the safety and potential for efficacy of intrapleural HSV1716 in patients with inoperable MPM.

Methods: We performed an open label, dose escalation, phase I/IIa trial of intra-pleural HSV1716. Patients with a histological diagnosis of MPM and indwelling pleural catheter (IPC) were eligible if they had performance status $\leq$ 2 and adequate hematologic, renal and liver function. Patients received 1x10^7pfu HSV1716 through their IPC on 1, 2 or 4 occasions a week apart, in 3 separate cohorts. The primary objective was to determine the safety and tolerability of intra-pleural HSV1716. The secondary objectives were to assess HSV1716 replication and patient immune responses in pleural fluid and blood. An exploratory objective was to assess tumour response by CT, using modified RECIST criteria.

Results: Twelve patients were treated, 3 received 1 dose of intrapleural HSV1716, 3 received 2 doses and 6 received 4 doses. HSV1716 was well-tolerated with no HSV1716-related SAE and 17 HSV1716-related transient Grade 1-2 AEs. Evidence of HSV1716 replication (n = 9) and pleural Th1 cytokine responses (n = 8) were observed. Novel anti-tumor IgG responses were detected post treatment and their antigen targets identified by protein array. CT analysis on day 57 indicated 6 patients with stable and 6 patients with progressive disease. Median survival from treatment was 15mths for all patients and 18mths in patients with evidence of a Th1 immune response (n = 8).

Conclusions: The study demonstrated an acceptable safety profile of intra-pleural HSV1716 with evidence of viral replication and anti-tumour immunogenicity. This supports further studies in MPM, possibly involving combination with immune checkpoint inhibitors.

Clinical trial identification: NCT01721018

Legal entity responsible for the study: Virttu Biologics Ltd

Funding: Virttu Biologics Ltd

Disclosure: S. Danson: Advisory role for Incathera Research funding from Lilly, GSK, Bristol-Myers Squibb, Astellas, Incyte, Novartis, Boehringer. P. Woll: Consulting/Advisory role to Lilly, Theradex. Research funding from AstraZeneca, Pfizer, Virttu. P. Fisher: Consulting/Advisory Role to Diaceutics. Research Funding from Pierre Fabre, Pfizer, Bristol-Myers Squibb. J. Roman, K. Simpson, R. Spavin, K. Learmonth, J. Conner: Employee of Virttu Biologics. All other authors have declared no conflicts of interest.

367PD Early FDG-PET response correlates with dose and clinical efficacy in patients with microsatellite stable (MSS) metastatic CRC (mCRC) treated with the CEA-CD3 T-cell bispecific antibody plus atezolizumab

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Background: CEA-CD3 TCB (RG7802, RO6958688) is a novel T-cell bispecific antibody targeting CEA on tumor cells and CD3 on T cells. An ongoing phase Ib study (NCT02650713) is exploring the safety, tolerability and efficacy of CEA-CD3 TCB in combination with atezolizumab. We report preliminary results of FDG-PET imaging as an early pharmacodynamic marker for this novel cancer immunotherapy combination in MSS mCRC patients.

Methods: In this study, CEA-CD3 TCB is given QW in combination with atezolizumab 1200 mg Q3W in patients with CEA-expressing solid tumors. As of March 3, 2017, a total of 35 MSS mCRC patients have been treated with CEA-CD3 TCB doses of 5-160 mg; 15 patients were evaluable for PET image analysis. On-treatment FDG-PET scans were performed at week 4 and compared with baseline. On-treatment changes in SUV_{max}, metabolic tumor volume (MTV) and total lesion glycolysis (TLG) were

analyzed in up to 10 measurable lesions per patient, identified at baseline by an independent reviewer. The exploratory statistical analyses used semiparametric Gaussian regression models and Cox PH landmark analyses (for progression-free survival [PFS]).

Results: Early changes in FDG-PET parameters showed a dose-response relationship (MTV: $P = 0.0022$; TLG: $P = 0.0054$; SUV_{max}: $P = 0.0081$); notably all patients receiving doses $\geq$ 80 mg (n = 7) showed decreases in SUV_{max}, TLG and MTV at week 4. Furthermore, week 4 reductions in FDG uptake (MTV: $P < 0.001$; TLG: $P < 0.001$; SUV_{max}: $P = 0.0061$) correlated with later tumor shrinkage (best change from baseline per RECIST v1.1). Reduction in MTV and TLG, but not SUV_{max}, correlated with decreases in soluble CEA levels measured at week 6 (MTV: $P = 0.013$; TLG: $P = 0.034$; SUV_{max}: $P = 0.54$) and longer PFS (MTV: $P = 0.013$; TLG: $P = 0.052$; SUV_{max}: $P = 0.85$).

Conclusions: In MSS mCRC patients, changes in MTV, TLG and SUV_{max} correlated with dose and tumor shrinkage. Decreases in 2 FDG parameters (MTV and TLG) correlated with a reduction in soluble CEA levels. Early on-treatment changes in FDG-PET can serve as a pharmacodynamic biomarker related to treatment efficacy.

Clinical trial identification: NCT02650713

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

Funding: F. Hoffmann-La Roche Ltd.

Disclosure: F. Sandoval, D. Sabanes Bove, S. Bouseida, V. Karanikas, A. Keelara: Roche employee. J. Saro: Employee of Roche and stock holder of Roche. T. Nayak: Roche stock.

368PD Dose escalation/expansion study to investigate the safety, pharmacokinetics, food effect, and antitumor activity of BGB-290 in patients with advanced solid tumors

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Background: Poly (ADP-ribose) polymerase inhibitors (PARPis) represent a class of antitumor agents that exert their cytotoxic effects by inhibiting PARP activity. Some PARPis are capable of trapping PARP proteins on DNA further augmenting cell death. BGB-290 is a potent and selective PARP1/2 inhibitor with strong PARP-trapping and antitumor activity in both *in vitro* and *in vivo* preclinical tumor models harboring *BRCA* gene mutations or other homologous recombination defects.

Methods: This two-staged study (NCT02361723) consists of a Phase 1A dose-escalation/dose-finding component to establish the maximum tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D) of BGB-290 in patients with solid tumors and a two-part Phase 2 component that includes expansion in targeted indications (Part A) and the effect of food on the BGB-290 pharmacokinetic (PK) profile (Part B).

Results: As of 1 May 2017, Phase 1A had completed enrollment (n = 45); 3 patients remain on treatment. Objective responses were observed across the dose range (2.5–120 mg BID). Of the 23 evaluable patients with gynecological cancer, 10 (43%) achieved an objective response per RECIST 1.1 (n = 3 complete; n = 7 partial). More patients with germline *BRCA 1/2* mutated ovarian cancer achieved an objective response (n = 7/12, 58%) than patients not carrying the mutation (n = 2/8, 25%). Drug-related adverse events (AEs) reported in $\geq$ 10% of patients were nausea, fatigue, anemia, vomiting, diarrhea, anorexia and neutropenia. Anemia and neutropenia were the most common drug-related Grade 3 AEs; no Grade 4 drug-related AEs were reported. Three BGB-290-related serious AEs were reported (anemia, n = 2; nausea, n = 1). Four deaths were associated with an AE; however, none were considered drug-related. The BGB-290 RP2D was determined as 60 mg BID and is being evaluated in Phase 2 to determine antitumor activity and food effects. Dose escalation to determine MTD with QD dosing is ongoing.

Conclusions: BGB-290 has demonstrated a favorable safety profile and promising preliminary antitumor activity in phase 1A; phase 2 is ongoing evaluating in patients with ovarian, breast, prostate, gastric and small cell lung cancer.

Clinical trial identification: NCT02361723, January 29, 2015

Legal entity responsible for the study: Beigene Ltd.

Funding: Beigene Ltd.

Disclosure: T. Meniawy: Non-financial support and other from Beigene during the conduct of the study. T. Tang, R. Wei, M. Li, V. Paton: Employee of BeiGene. All other authors have declared no conflicts of interest.

370PD Phase I dose escalation study of M2698, a p70S6K/AKT inhibitor, in patients with advanced cancer

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Background: Aberrant PI3K/Akt/mTOR (PAM) pathway signaling is observed in various tumors and confers resistance to standard therapies. M2698 is an oral, brain penetrant, potent and selective p70S6K/Akt1/3 inhibitor that can block signaling from Akt feedback loop activation, a possible tumor escape mechanism

Methods: Patients (pts) with advanced cancer were given oral M2698 daily (PO 15–380 mg) in 21-day (d) cycles in a 3 + 3 dose escalation [DE] design. Response was assessed every 2 cycles. An expansion phase in pts with PAM pathway tumor alterations is ongoing

Results: Overall, 50 pts received M2698 monotherapy (DE, n = 40; expansion, n = 10); DE data presented only (cut-off 10/27/16). Treated pts had a median age of 56 years. (14 men, 26 women). Tumor types included breast (n = 7), colon (n = 4), lung (n = 4) and other (n = 25). In the DE phase, 35/40 pts were evaluable. Two pts had a dose limiting toxicity (DLT; 60mg and 160mg) and drug-related Grade $\geq$3 adverse events (AEs) occurred in 6/40 (15%) of pts. AEs leading to dose reductions occurred in 1 pt at < 320 mg/d and in 3 pts $\geq$320 mg/d. Of the 32 DE pts (without DLT) who completed treatment by the data cut-off, 6 pts (19%) remained on treatment (Rx) for $\geq$ 180 days (min, max range 21 to 504 days) [Table]. Exposure of M2698 increased dose proportionally and ^{3}80% phospho-S6 inhibition in tumor was achieved in 2/7 paired biopsies from pts treated with doses ^{3}110 mg/d. Expansion phase dose was 240 mg/d PO. Tissue molecular analysis and liquid biopsies were performed. Analysis is ongoing.

Table: 370PD

Dose level mg/d	All Pts in DE set without DLT	
	N	Days on Rx
15	3	90, 126, 42
30	3	504, 126, 112
60	5	42, 42, 21, 180, 42
75	3	42, 42, 84
110	3	462, 42, 42
160	5	42, 42, 223, 42, 62
200	3	215, 73, 126
320	6	75, 256, 41, 168, 98, 70
380	2	42*

1 pt on treatment at data cut off.

Conclusions: M2698 was well tolerated and provided stable disease over a wide range of doses.

Clinical trial identification: NCT01971515

Legal entity responsible for the study: Merck KGaA, Darmstadt, Germany

Funding: Merck KGaA, Darmstadt, Germany

Disclosure: G. Lopes, R. Kurzrock: Research funding from Merck. A. Victor: Merck employee. J. Shaw, R. Kaleta: EMD Serono employee. All other authors have declared no conflicts of interest.

371PD A Phase 1 PK/PD Study of ASN003, a novel highly selective BRAF and PI3K inhibitor, in patients with advanced solid tumors

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Background: RAS-RAF-MEK and PI3K-AKT-mTOR are two major pathways involved in tumor cell signaling and growth. Components of these pathways are frequently mutated in a broad range of tumors. ASN003 is a highly selective and potent (low nM IC_{50}) inhibitor of BRAF and PI3K-α and -d (low affinity for PI3K-b). ASN003 shows strong antitumor activity in tumor models harboring BRAF and PIK3CA or PTEN mutations, and also in PDX models that are resistant to selective BRAF and MEK inhibitors.

Methods: Oral ASN003 once daily is being evaluated for safety/tolerability and preliminary efficacy in eligible patients with advanced solid tumors using an accelerated dose titration design (Part A) and enrolling cohorts of melanoma, CRC and NSCLC patients with a BRAF, PIK3CA or PTEN mutation at MTD (Part B). Eligibility criteria include HbA1c ≤ ULN or fasting glucose <140 mg/dL. Pharmacokinetic (PK) profile and the pharmacodynamic (PD) effects of ASN003 on tumor tissue biomarkers such as pERK and pS6 are investigated in both parts of the study.

Results: Patient accrual is ongoing. To date, seven eligible patients are enrolled in dose levels ranging from 10 – 120 mg QD. ASN003 has been well tolerated. Treatment-related adverse events (TRAEs) were mild (G1) to moderate (G2). TRAEs include diarrhea (G2) (n = 1), nausea/vomiting (G1) and dry mouth/lips/skin (G1). Transient G1 elevation of glucose and insulin c-peptide levels has been noted in 1 pt. No G3/4 AEs have been observed to date. The PK profile showed excellent, systemic exposure at steady state at all doses (C_{max} up to 930 ng/mL, $AUC_{0\text{-}T}$ up to 18998 ng.h/mL at 80 mg QD) and a half-life of > 12 hour. Dose escalation is ongoing.

Conclusions: ASN003 is a novel small molecule, with uniquely selective and potent inhibition of BRAF, PI3-α and -d kinases. To date, ASN003 was well tolerated at doses up to 120 mg QD and achieved good systemic exposure. Updated and detailed clinical safety/efficacy and PK/PD results will be presented.

Clinical trial identification: NCT02961283

Legal entity responsible for the study: Asana BioSciences

Funding: Asana BioSciences

Disclosure: S. Reddy, N. Rao, L. Denis: Employee and Stock Ownership Asana BioSciences. A. Tolcher, K.T. Flaherty: Member of Scientific Advisory Board Asana BioSciences. All other authors have declared no conflicts of interest.

372PD First-in-human (FIH) study of TAS-120, a highly selective covalent oral fibroblast growth factor receptor (FGFR) inhibitor, in patients (pts) with advanced solid tumors

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Background: Dysregulation of the FGF/FGFR signaling pathway has been associated with many developmental disorders and varieties of cancers. TAS-120 is an oral, highly selective covalent FGFR inhibitor with potent antitumor activity *in vitro* and *in vivo* models with FGFR pathway aberration.

Methods: This FIH study consists of dose escalation phase (DE) and expansion phase (EX). The objectives of this study are to determine the maximum tolerated dose (MTD)/recommended dose (RD) and to investigate the safety, pharmacokinetics, pharmacodynamics, and efficacy. In DE, the first three cohorts were evaluated by a single patient then a 3 + 3 design is used which is currently ongoing. Pts with FGFR abnormalities can be enrolled to EX during the evaluation of DE with dose lower than maximum administered dose under evaluation. TAS-120 was administered orally three times weekly (Monday-Wednesday-Friday) in a 21day cycle.

Results: As of 3 Apr 2017, 36 pts (34% FGFR with genetic abnormalities) were enrolled (DE; 26 pts, EX; 10 pts). Tumor types enrolled were bladder cancer (n = 8), colorectal cancer (n = 7), biliary tract cancer (n = 4), gastric, esophageal and pancreas cancer (n = 3 each), and others (n = 8). Pts were treated in 8 dose cohorts of 8 -160 mg. MTD has not been reached. The most common drug-related AEs (all AEs ≥10%) were hyperphosphatemia (79%), and anorexia (12%). Grade ≥3 hyperphosphatemia has never been observed. Hyperphosphatemia was managed with dose interruption or reduction in addition of phosphate binders. Drug-related SAE has not occurred. TAS-120 exposure increased with dosage. Mean C_{max} and $AUC_{0\text{-}48}$ at 160 mg were 1,192 ng/mL and 9,972 ng*h/mL, respectively, with a mean T_{max} of 2.67 hrs and apparent $T_{1/2}$ of 6.06 hrs. Two pts showed the clinical response, one of them was gastric cancer with FGFR2 amplification at 80 mg, and the other was esophageal cancer (FGFR status is under evaluation) at 120 mg. Moreover, two biliary tract cancer with FGFR2 fusion at 56 mg, and one bladder cancer at 36 mg (FGFR status is unknown) had stable disease > 24 weeks.

Conclusions: TAS-120 was well-tolerated, and the safety profile was confirmed up to 120 mg. The ongoing DE and EX are still under evaluation and RD will be determined.

Clinical trial identification: Clinical trial information: JapicCTI-142552

Legal entity responsible for the study: TAIHO Pharmaceutical co., LTD.

Funding: TAIHO Pharmaceutical co., LTD.

Disclosure: Y. Kuboki: Honoraria: Taiho Pharmaceutical, Bayer. N. Matsubara: Advisory Board: Janssen, AstraZeneca. Corporate-sponsored research: Janssen, Bayer. Honoraria: Taiho Pharmaceutical. Speakers' Bureau: Janssen, AstraZeneca, Sanofi. H. Bando: Corporate-sponsored research: AstraZeneca, Sysmex, FALCO Biosystems. Speakers' Bureau: Taiho Pharmaceutical, Lilly, Takeda, Merck Serono, Chugai, Yakult. K. Shitara: Advisory Board: Bayer, Chugai, Lilly, Takeda. Corporate-sponsored research: Bayer, Chugai, Dainippon Sumitomo, Lilly, MSD, Sanofi, Daiichi Sankyo, Taiho, Yakult. Honoraria: Bayer, Chugai, Bristol-Myers Squibb, Novartis, Takeda. K. Yoh: Corporate-sponsored research: AstraZeneca, Lilly, Taiho Pharmaceutical, Pfizer. Honoraria: AstraZeneca, Chugai, Boehringer Ingelheim, Lilly, Bristol-Myers Squibb, Taiho Pharmaceutical, Ono Pharmaceutical. T. Kojima: Corporate-sponsored research: AstraZeneca, Ono Pharmaceutical, Shionogi, MSD, Merck Serono, Taiho Pharmaceutical. Speakers' Bureau: Chugai. I. Ohno: Advisory Board: Merck Serono. H. Takahashi: Corporate-sponsored research: Bayer, Bristol-Myers Squibb. Honoraria: Taiho Pharmaceutical. S. Kondo: Corporate-sponsored research: AstraZeneca, Lilly, Pfizer, ASLAN, Merck Serono. H. Hirai: Employee: Taiho Pharmaceutical. C. Morizane: Advisory Board: AstraZeneca, Yakult, Novartis, Taiho. Corporate-sponsored research: GlaxoSmithKline, Pfizer, Nobelpharma, Eisai, Yakult, Ono, Taiho. Honoraria: Pfizer, Novartis, Yakult, Lilly, Nobelpharma, Fujifilm. T. Doi: Advisory Board: Lilly, Chugai, Kyowa Hakko Kirin, Novartis, MSD, Daiichi Sankyo, Amgen. Corporate-sponsored research: Taiho, Merck, Astellas, Janssen, Takeda, Pfizer, Lilly, Sumitomo Group, Bayer, Chugai, Kyowa Hakko Kirin, Boehringer, Novartis, MSD, Daiichi Sankyo, Celgene. All other authors have declared no conflicts of interest.

373PD Phase 1 Study of E7046, a PGE2 Receptor EP-4 inhibitor that targets immunosuppressive myeloid cells in the tumor microenvironment

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Background: E7046 is a selective small molecule antagonist of the prostaglandin E_2 receptor-type-4 that inhibits the differentiation of monocytic myeloid lineage cells towards a pro-tumorigenic phenotype in the TME. This is a first-in-human study of single-agent E7046.

Methods: Key eligibility criteria: patients (pts) ≥18 years with selected advanced cancers with high levels of myeloid infiltrate. The dose-escalation phase consisted of 6-pt cohorts of 125, 250, 500, and 750 mg (once-daily, oral, 21-day cycle) doses of E7046. Primary objectives were safety/tolerability, maximum tolerated dose (MTD) and/or RP2D. Secondary objectives included PK and initial anti-tumor activity; exploratory objectives included PD assessments on immune cells in tumor infiltrate and in peripheral blood and metabolic response by ^{18}FDG-PET.

Results: 30 pts received E7046 (median age 58 yrs [24-78]; 2-7 lines of prior therapy). Most common tumor types were colorectal cancer (40%), pancreatic cancer (20%), and SCCHN (13%). No DLTs were observed and the MTD was not reached. The most frequent drug-related adverse events (AEs) were diarrhea (20%), decreased appetite, fatigue and nausea (13% each). Drug-related AEs of Gr 3/4 occurred in 4 pts (diarrhea, anaphylactic reaction, hypersensitivity, hyperuricemia, rash, generalized rash). 2 pts had drug-related serious AEs (rash, allergic reaction, fever in 1 pt; hyperuricemia, acute renal failure [Gr 2] in 1 pt). 3 pts discontinued treatment due to AEs (bowel obstruction, allergic reaction, abdominal pain). There were no drug-related deaths. E7046 exposure was dose proportional up to 500 mg with no incremental increase in exposure at 750 mg. E7046 was extensively metabolized, elimination half-life was ∼12hr and accumulation on multiple dosing was ∼2-fold. 2 pts are ongoing and preliminary efficacy showed no objective responses, 4 pts with durable SD or clinically stable (>4 mo) and 4 pts with ^{18}FDG-PET metabolic responses.

Conclusions: Single-agent E7046 was tolerated with no MTD reached in heavily pretreated pts with myeloid-rich tumors. PD analysis of immune cell modulation to help determine the RP2D will be presented at the meeting.

Clinical trial identification: NCT02540291

Legal entity responsible for the study: Eisai Inc.

Funding: Eisai Inc.

Disclosure: D.S. Hong: Research/Grant Funding: Bayer, Lilly, Genentech, LOXO, Pfizer, Amgen, Mirati, Ignyta, Merck, Daichi-Sanko, Eisai. Travel/Accommodations: MiRNA, LOXO. Consulting/Advisory: Bayer, Baxter, Guidepoint Global. Other interests: Oncoreseponse (founder). L. Reyderman, M. Ren, T. Binder, C.E. Ooi, S. Dayal, O. Ataman: Employee of Eisai Ltd. A. Marabelle: Clinical trial funding from Eisai. Consulting fees from Eisai and Roche. Funding for anti-CSF1R clinical trial from Roche. All other authors have declared no conflicts of interest.

374PD A first in human phase 1 study of KPT-9274, a first in class dual inhibitor of PAK4 and NAMPT, in patients with advanced solid malignancies or NHL

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Background: KPT-9274 is an oral, small molecule modulator of PAK4 (p21 activated kinase) and NAMPT (nicotinamide phosphoribosyltransferase). PAK4 is a major player in cell morphology and WNT/β-catenin signaling. NAMPT is the rate-limiting enzyme in NAD biosynthesis. Co-inhibition of these targets leads to synergistic anti-tumor effects through energy depletion, inhibition of DNA repair, cell cycle arrest, and ultimately apoptosis. Cells can utilize niacin to make NAD through an alternative pathway using NAPRT1. NAPRT1 is often absent in tumors making it a potential response biomarker. KPT-9274 demonstrates potent anti-tumor activity pre-clinically and in patient dogs with cancer.

Methods: This dose escalation study evaluates KPT-9274 as a single agent and co-dosed with niacin. KPT-9274 is given QoDx3/week (28-day cycle) at a starting dose of 10 mg. The objectives are to evaluate safety and tolerability of KPT-9274, dose-limiting toxicities (DLT), maximum tolerated dose (MTD), recommended phase 2 dose, early anti-tumor activities, pharmacokinetic (PK) and pharmacodynamic properties.

Results: As of 02-Mar-17, 14 patients (pts: 9M/5F; median age 61) with advanced solid tumors were enrolled in 4 cohorts (10 – 40 mg). One DLT (G4 anemia) at 40 mg was reported. MTD is not yet reached. Drug-related adverse events (AEs) include G2-4 anemia (6 pts, 43%) and G3 fatigue (1 pt, 7%). The most common G2 AEs are arthralgia and myalgia (3 pts; 21% each) and influenza-like illness (2 pts; 14%). Stable disease (SD) was seen in 29% of the 14 pts. Preliminary PK analysis suggests plasma exposure was dose proportional on C1D1 increasing 4 to 5-fold by C1D24. On C1D24, the mean C_{max} and AUC_{0-t} observed in 20 – 30 mg cohorts were 319 – 1,573 ng/mL and 10,456 – 59,152 ng*hr/mL, respectively. Preliminary data indicate that treatment of KPT-9274 reduces NAD levels vs. baseline in circulating leukocytes and tumor biopsies. Analyses to correlate NAPRT1 status with response is ongoing (2 of 4 SD pts are NAPRT1-).

Conclusions: Oral KPT-9274 is tolerated in pts with advanced solid malignancies. Anemia, arthralgias and myalgias are common AEs with one DLT (G4 anemia). PK is generally proportional and predictable.

Clinical trial identification: NCT02702492

Legal entity responsible for the study: Karyopharm Therapeutics Inc

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375PD Phase I study of the checkpoint kinase 1 inhibitor GDC-0575 in combination with gemcitabine (gem) in patients (pts) with refractory solid tumors

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Background: Checkpoint kinase 1 (Chk1) inhibition following chemotherapy overrides cell cycle arrest and induces mitotic catastrophe and cell death. GDC-0575 is a highly-selective oral small-molecule Chk1 inhibitor that results in tumor shrinkage and growth delay in xenograft models.

Methods: This Phase I trial enrolled pts with refractory solid tumors and ECOG 0-1 status. Patients received IV gem 1000 mg/m^2 followed ∼24 hours later by GDC-0575 (15-60 mg) PO, or IV gem 500 mg/m^2 followed ∼24 hours later by GDC-0575 (45-105 mg) PO, weekly for 2 of 3-week cycles. TP53 was evaluated in archival tumor tissue by gene sequencing. Safety, pharmacokinetics (PK), pharmacodynamics, and tumor response by RECIST v1.1 were investigated.

Results: Of 81 pts treated, 73% were female, the median age was 56 years (range 27-75), and 48% were ECOG PS 0. The most common tumor types were breast (46%), and soft tissue sarcoma and NSCLC (both 7%). Dose escalation was halted at GDC-0575 60 mg and 105 mg with gem 1000 mg/m^2 and gem 500 mg/m^2, respectively, as pts experienced Grade 4 thrombocytopenia and Grade 3-4 febrile neutropenia as dose-limiting toxicities. The most frequent adverse events (all grades) related to GDC-0575 and/or gem were neutropenia (80%), anemia (56%), fatigue (47%), nausea (46%), and thrombocytopenia (40%). Maximum concentrations of GDC-0575 were achieved within 2 hours of dosing, and its half-life was ∼23 hours. No PK drug-drug interaction was observed between GDC-0575 and gem. Among pts treated with GDC-0575 and gem 500 mg/m^2, there were 4 cPRs (2x sarcoma, NSCLC, TNBC) and 3 SDs (TNBC, NSCLC, SCLC) for $\geq$ 6 months. Exome sequencing data from tumor samples obtained at progression did not reveal mutations in Chk1 but identified mutations in genes known to regulate apoptosis.

Conclusions: The Chk1 inhibitor GDC-0575 can be safely combined with a standard or modified dose and schedule of gem. Hematological toxicities were frequent but manageable. Preliminary anti-tumor activity was observed in patients with a variety of refractory solid tumors treated with GDC-0575 in combination with gem 500 mg/m^2.

Clinical trial identification: NCT01564251

Legal entity responsible for the study: Genentech, Inc.

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376P Preclinical evaluation of the anti-CLDN18.2 antibody, IMAB362, in pancreatic carcinoma

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Background: Claudin 18.2 (CLDN18.2) is a tight junction protein restricted to the gastric mucosa cells; however, in the context of malignant transformation CLDN18.2 can be found in tumors derived from organs that do not normally express CLDN18.2, such as the pancreas. IMAB362 is a first-in-development monoclonal antibody that specifically targets CLDN18.2-expressing tumor cells. The aims of this preclinical study were to examine CLDN18.2 expression in pancreatic cancer (PC) and to evaluate IMAB362 as a single agent or in combination with standard chemotherapy for the treatment of PC.

Methods: CLDN18.2 expression in normal and neoplastic pancreatic tissues from patients with PC was assessed by a validated, semi-quantitative, IHC assay. IMAB362 pharmacodynamics, including binding characteristics, antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), and IMAB362-induced antitumor activity, were assayed in vitro (human PC cell lines) and in vivo (PC xenograft mouse models).

Results: CLDN18.2 expression levels and patterns in normal and malignant pancreatic tissue were very different. Whereas CLDN18.2 was not observed in normal tissue, CLDN18.2 was expressed in about 50% of tested neoplastic pancreatic tissues and pre-malignant lesions. IMAB362 bound with high specificity and high affinity to CLDN18.2-positive (CLDN18.2$^+$) PC cells. IMAB362-induced efficient lysis of CLDN18.2$^+$ PC cells through ADCC. In vitro, pretreatment of human PC cells with chemotherapeutic agents resulted in CLDN18.2 stabilization and a higher epitope density, which led to an increase in IMAB362-induced ADCC. Repeated doses of IV IMAB362 in mice bearing CLDN18.2$^+$ PC xenografts resulted in slowed tumor growth and survival benefit. In vitro studies and animal data showed the antitumor activity of IMAB362 to be further augmented by pretreatment with gemcitabine and gemcitabine plus oxaliplatin.

Conclusions: In these preclinical studies, IMAB362 induced cell death in CLDN18.2$^+$ human PC cell lines and xenografted tumors, and demonstrated potential as a targeted treatment for PC, both as single agent and in combination with chemotherapy.

Legal entity responsible for the study: Ganymed Pharmaceuticals AG, A company of Astellas Pharma, Inc

Funding: Ganymed Pharmaceuticals AG, A company of Astellas Pharma, Inc

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377P Preclinical characterization of IMAB362-vcMMAE, an anti-CLDN18.2 antibody–drug conjugate

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Background: Antibody–drug conjugates combine the specific targeting and antitumor activity of monoclonal antibodies with the potent cell killing activity of cytotoxic small molecule drugs. IMAB362 is a monoclonal antibody specific for the tight junction protein Claudin 18.2 (CLDN18.2). In normal tissue, CLDN18.2 is exclusively expressed in the gastric mucosa. In the context of malignant transformation, CLDN18.2 can be found in gastric tumors as well as tumors from organs that do not normally express CLDN18.2 (eg, pancreas). Preclinical characterization of IMAB362 conjugated to the antimitotic molecule, monomethyl auristatin E, with a valine–citrulline linker (IMAB362–vcMMAE) is presented here.

Methods: IMAB362–vcMMAE binding characteristics and internalization were assessed in CLDN18.2-expressing human cell lines. Cell viability and IMAB362–vcMMAE-mediated cytotoxic effects (direct and indirect [bystander]) were also assessed in CLDN18.2 in vitro models. Xenograft mouse models of pancreatic and gastric cancers were developed to assess the cytotoxic and antitumor effects of IMAB362–vcMMAE in vitro.

Results: IMAB362–vcMMAE showed a slightly decreased relative binding affinity on CLDN18.2-transfected cells and cells that endogenously express CLDN18.2 compared with unconjugated IMAB362. In cell lines that internalized IMAB362–vcMMAE, cell viability was reduced by 45–90%; EC_{50} negatively correlated with CLDN18.2 expression level, with the lowest EC_{50} being <30 ng/mL. By contrast, no reduction in cell viability occurred in cells without target expression. IMAB362–vcMMAE produced CLDN18.2-negative cell death via bystander effect in vitro (co-cultured tumor cells). In vivo, intravenous IMAB362–vcMMAE resulted in dose-dependent inhibition of tumor growth as well as prolonged survival in early and advanced tumors in both pancreatic and gastric cancer mouse models; significant antitumor activity was observed after a single 8 or 16 mg/kg IV bolus injection. No systemic or organ-specific IMAB362–vcMMAE-related toxicity was observed in the mice.

Conclusions: IMAB362–vcMMAE is a highly specific and potent antibody-drug conjugate against in vivo and in vitro models of gastric and pancreatic cancers.

Legal entity responsible for the study: Ganymed Pharamaceuticals AG, A company of Astellas Pharma, Inc

Funding: Ganymed Pharamaceuticals AG, A company of Astellas Pharma, Inc

Disclosure: M. Kreuzberg: Emplyee of Ganymed Pharamceuticals AG, a company of Astellas Pharma, Inc. R. Mitnacht-Kraus: Employee of Ganymed Pharmaceuticals AG, a company of Astellas Pharma, Inc. In addition, Dr. Mitnacht-Kraus has a patent P-24PCT issued, a patent P-33PCT issued, a patent P-34PCT issued, and a patent P-36PCT issued. U. Sahin: Stock option owner, ex-shareholder and cofounder of Ganymed Pharmaceuticals AG and Founder/CEO/shareholder of Biontech Holding outside the submitted work. Dr. Sahin has several patents issued to this work that have been acquired by Astellas. Ö. Türeci: Stock option owner, ex-shareholder, cofounder & CEO of Ganymed Pharmaceuticals AG, has received consultancy fees from Astellas, and has several patents issued to this work that have been acquired by Astellas.

378P Preclinical characterization of IMAB362 for the treatment of gastric carcinoma

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Background: Monoclonal antibodies (mAbs) are a key component of cancer therapy. An ideal therapeutic mAb would selectively bind to cancer cells while avoiding binding to healthy tissue. In normal tissue, Claudin 18.2 (CLDN18.2) is expressed in gastric mucosal cell tight junctions, largely inaccessible to mAbs. Upon malignant transformation, perturbations in cell polarity lead to cell surface exposure of CLDN18.2 making it targetable by mAbs. This has driven the development of an anti-CLDN18.2 mAb, IMAB362, which specifically targets CLDN18.2-positive cancer cells while sparing normal tissue. The preclinical characterization of IMAB362 as a targeted therapy for gastric cancer (GC) is presented here.

Methods: CLDN18.2 expression was characterized in primary tumors and metastases (32 of which corresponded to primary tumors) from GC patients using a validated, semi-quantitative, IHC assay. IMAB362 binding characteristics and mechanism of action were assessed in vitro using CLDN18.2-expressing cell lines and in vivo in mouse tumor xenografts. Antitumor activity of IMAB362 was assessed in human GC cell line xenografts in mice treated with chemotherapy with/without IMAB362.

Results: In patient-derived GC tissue, CLDN18.2 was frequently (~80%) and robustly expressed in both primary and metastatic tumors. IMAB362 was highly selective for CLDN18.2 both in vivo and in vitro. IMAB362 mediated effective and target-selective antibody-dependent cellular cytotoxicity (ADCC) against GC cell lines with endogenous CLDN18.2 expression and induced complement-dependent cytotoxicity (CDC)-mediated lysis of CLDN18.2-expressing tumor cells. IMAB362-mediated ADCC and CDC were not affected by the presence of CLDN18.2-negative cancer cells. Treatment with chemotherapy sensitized tumor cell lines to IMAB362-mediated mechanisms by increasing CLDN18.2 expression; improved antitumor activity was observed in xenografted mice treated with IMAB362 + chemotherapy compared with mice treated with chemotherapy alone.

Conclusions: IMAB362 is a target-selective mAb with strong immune effector mediated antitumor activity (ADCC, CDC) that contributes to the elimination of CLDN18.2-expressing GC cells and synergizes with chemotherapy.

Legal entity responsible for the study: Ganymed Pharmaceuticals AG, A company of Astellas Pharma, Inc A company of Astellas Pharma Inc Ganymed Pharmaceuticals GmbH A company of Astellas Pharma Inc Ganymed Pharmaceuticals GmbH A company of Astellas Pharma Inc Ganymed Pharmaceuticals AG, A company of Astellas Pharma Inc

Funding: Ganymed Pharmaceuticals AG, A company of Astellas Pharma, Inc A company of Astellas Pharma Inc Ganymed Pharmaceuticals AG, A company of Astellas Pharma, Inc

Disclosure: R. Mitnacht-Kraus: Employee of Ganymed Pharmaceuticals AG, a company of Astellas Pharma, Inc. In addition, Dr. Mitnacht-Kraus has a patent P-24PCT issued, a patent P-33PCT issued, a patent P-34PCT issued, and a patent P-36PCT issued. M. Kreuzberg: Employee of Ganymed Pharamceuticals AG, a company of Astellas Pharma, Inc. M. Utsch: Employee of Ganymed Pharmaceuticals AG, a company of Astellas Pharma, Inc. In addition, Dr. Utsch has a patent PCT/EP2012/002210 issued. U. Sahin: Stock option owner, ex-shareholder and cofounder of Ganymed Pharmaceuticals AG and Founder/CEO/shareholder of Biontech Holding outside the submitted work. Dr. Sahin has several patents issued to this work that have been acquired by Astellas. Ö. Türeci: Stock option owner, ex-shareholder, cofounder & CEO of Ganymed Pharmaceuticals AG, has received consultancy fees from Astellas, and has several patents issued to this work that have been acquired by Astellas.

379P A novel mRNA-based patient selection strategy identifies fibroblast growth factor receptor (FGFR) inhibitor-sensitive tumors: Results from rogaratinib Phase-1 study

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Background: Altered FGFR signaling is a potential target for anticancer therapy. Rogaratinib (BAY1163877) is an oral inhibitor of FGFRs 1-4. Screening for patients based on tumor FGFR1-3 mRNA overexpression, we reported in a phase I study that selected urothelial carcinoma patients were highly sensitive to rogaratinib treatment (NCT01976741; Joerger et al, ESMO 2016). Here we further identify patients sensitive to rogaratinib with malignancies not previously identified as being driven by FGFRs.

Methods: Subjects with treatment-refractory advanced or metastatic solid tumors were screened for high FGFR1-3 mRNA expression levels by RNA *in situ* hybridization (RNAscope®; Advanced Cell Diagnostics, Inc., Newark, CA) and Nanostring® assay (NanoString Technologies, Inc., Seattle, WA) from fresh or archival tumor specimens. FGFR-positive patients were treated with 800 mg BID on a continuous 21-day cycle. Responses were assessed by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

Results: More than 500 patient biopsies were screened for FGFR1-3 mRNA levels. Seventy two FGFR-positive patients were treated with rogaratinib, with 63 evaluable for response. Clinical responses were observed in tumor types not previously associated with FGFR alterations, including a partial remission (PR) in a patient with a FGFR1 mRNA-positive adenoid cystic carcinoma of the tongue and a PR in a FGFR3 mRNA-

positive head and neck squamous cell carcinoma patient. Long-lasting stable disease with tumor shrinkage was also seen in patients with a) FGFR3 mRNA-positive gastric cancer, b) FGFR3 mRNA-positive lung squamous cell carcinoma c) FGFR3 mRNA-positive lung adenocarcinoma, d) FGFR2 mRNA-positive breast cancer and e) FGFR1 mRNA-positive hemangioendothelioma with complete disappearance of edema over 18 months.

Conclusions: Patient selection for treatment with rogaratinib based on quantification of FGFR1-3 mRNA isoforms in all tumor types irrespective of underlying data on DNA alterations is feasible and yields clinically meaningful responses in tumor types not been previously associated with altered FGFR signaling.

Clinical trial identification: NCT01976741

Legal entity responsible for the study: Bayer AG

Funding: Bayer AG

Disclosure: S. Bender, P. Ellinghaus, M. Ocker: Employment: Bayer AG. S. Ince, P. Rajagopalan: Employment: Bayer HealthCare Pharmaceuticals. All other authors have declared no conflicts of interest.

380P A phase 1b study evaluating the safety and pharmacokinetics (PK) of regorafenib (REG) in combination with cetuximab (CTX) in patients with advanced solid tumors

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Background: Combining REG with CTX may overcome intrinsic and acquired resistance in EGFR-sensitive and -resistant tumors. We evaluated the safety, PK, maximum tolerated dose (MTD), and preliminary efficacy of REG plus standard dose of CTX (initial 400 mg/m^2 intravenously followed by 250 mg/m^2 weekly) in a phase 1b study. Final results from the intermittent REG dosing arm (3 weeks on/1 week off) are reported, with final results from the terminated continuous REG dosing arm (n = 11) previously presented (Weekes et al. AACR 2016, abstract CT148).

Methods: This was an open-label, dose-escalation (3 + 3 design) study in patients with locally advanced or metastatic solid tumors who progressed after standard therapy. The starting dose of REG was 120 mg once daily (QD) in a 28-day cycle (3 weeks on/1 week off) plus CTX. If tolerable, REG was escalated to 160 mg QD. If not tolerable, the REG dose was reduced to 80 mg QD. Dose-limiting toxicities (DLTs) were evaluated in Cycle 1. Adverse events (AEs) were graded according to NCI-CTCAE v4.03. Antitumor activity was assessed using RECIST v1.1.

Results: As of January 31, 2017, 31 patients received REG in an intermittent schedule plus CTX: 8 patients received REG 120 mg and 23 received REG 160 mg. One DLT of grade 3 hand–foot skin reaction was reported in 6 evaluable patients at the 120 mg dose level. No DLT was confirmed at the 160 mg dose level. The MTD was declared at the standard dose of REG 160 mg QD (3 weeks on/1 week off) plus the standard dose of CTX. The most common AEs, regardless of relationship to study drug, were hypophosphatemia (42%), fatigue (39%), and nausea (39%). The most common grade $\geq$3 REG-related AEs were hypophosphatemia (23%) and fatigue (10%). REG $AUC_{(0-tlast)}$ was 29.1 mg·h/L at 160 mg and 17.4 mg·h/L at 120 mg. CTX had no effect on the PK of REG. One patient (120 mg REG) had a partial response; 6 (160 mg REG; 29%) and 2 (120 mg REG; 25%) patients had stable disease.

Conclusions: REG at 160 mg QD (3 weeks on/1 week off) plus standard dose of CTX was tolerated with no unexpected toxicities. Observed AEs were in line with known REG and CTX safety profiles.

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Legal entity responsible for the study: Bayer

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381P Clinical study of apatinib in the treatment of malignant pleural effusion and malignant celiac effusion

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Background: Malignant pleural effusion and malignant celiac effusion is a severe complication of the advanced malignant tumor, The formation of malignant pleural effusion and malignant celiac effusion relied on VEGF growth factor.Apatinib blocking vascular endothelial growth factor (VEGF) combining with the receptor and blocking signal transduction pathway, thereby inhibiting tumor and the formation of new blood vessels, inhibit the formation of the malignant pleural effusion and malignant celiac effusion. We conducted the study to exploring the single-agent oral path of Apatinib for the treatment of malignant pleural effusion and malignant celiac effusion of the clinical curative effect.

Methods: Patients were eligible for inclusion in the study if they had histologically confirmed malignancies, with malignant pleural effusion and malignant celiac effusion. Eastern Cooperative Oncology Group (ECOG) performance status of 0-2. Study Objective: Clinical curative effect. Study Design and Treatment: This study recruited 13 patients with histologically confirmed malignancies, and the patients with malignant pleural effusion and malignant celiac effusion from January 2016 to October 2016. All patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2. All patients were given the oral drug Apatinib, the doses of oral given is 500 mg or 425 mg everyday until progressive disease (PD) or intolerable toxicity. Assessment and Statistical analysis: The assessmet were determined according to the World Health Organization (WHO) criteria. The ORR and DCR analyses were based on frequencies.

Results:

Table: 381P Baseline patient characteristics

Characteristic Apatinib(n = 13)
Age(years)
Median(range) 58(44-84) Sex Male 7(53.85) Female 6(46.15) EGOG PS 0 2(15.38) 1 6(46.15) 2 5(38.46) Carcinoma Lung cancer 6(46.15) Pancreatic cancer 4(30.77) Breast cancer 2(15.38) Thymic cancer 1(7.7)
Efficacy: Apatinib is effective for the treatment of malignant pleural effusion and malignant celiac effusion: CR 5 cases, PR 5 cases, SD 3 cases, overall-response rate (ORR)76.92%, disease-control rate (DCR)100%.

Conclusions: Apatinib is a safe, feasible way in the treatment of malignant pleural effusion and malignant celiac effusion. Relying on the simple method and favourable rencent curative effect. Apatinib provides a new way for the treatment of malignant pleural effusion and malignant celiac effusion that deserves further research.

Legal entity responsible for the study: GuoXin Ma

Funding: None

Disclosure: All authors have declared no conflicts of interest.

382P Evaluation of NRP-1 TM domain targeting peptide in melanoma

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Background: Membrane proteins and their interactions play central roles in a variety of cellular processes including nutrient uptake, signaling and cell-cell communication. Many cancers, neurological, metabolic and immune disorders can be attributed to the abnormal function of membrane proteins. All of these membrane proteins either contain one or several transmembrane (TM) strands and/or undergo some degree of oligomerization. Thus, stabilization or disruption of these protein-protein interactions is therefore of great interest for the modulation of protein function within the cell. In this context, TM domains of neuropilin-1 receptor (NRP1) and human epidermal growth factor receptor (HER2) are particularly studied in our laboratory to develop anti-cancer therapies based on the interference of the TM domains. Antitumor effects of TM peptides targeting NRP1 or HER2 has been proved in glioblastoma (Nasarre et al., 2010) and breast cancer (Arpel et al., 2016) respectively. In addition, HER2 has been proved to reduce metastasis in a metastatic model of breast cancer (Arpel et al., 2014). Moreover, NRP1 expression has been detected by immunostaining in tumor specimens obtained from patients with prostate, lung, pancreatic, colon carcinoma and melanoma.

Methods: In order to expand the therapeutic applications of these TM peptides, we evaluated its anti-tumoral activity in melanoma in an orthotopic allograft model in nude mice ($B_{16}F_{10}$ cell line).

Results: Our results show, that a local administration of MTP-NRP1 (1µg/kg, 3x/week) significantly reduces tumor development after 11 days of treatment. These results concur with the dT/dC% value at day 13 (18,3%) indicating that the treatment is efficiently impacting the tumor volume after this period. The application of the RECIST criteria identified 7.1% of mice presenting stable disease while 78,6% exhibited partial response. However 14.3% of mice were non responders to the treatment.

Conclusions: Hence, current work is conducted to analyze by gene array profiling the differences in NRP1 and other cancer promoting receptors between responder and non-responder populations. This is a prerequisite to decide whether MTP-NRP1 could be developed in this indication, particularly by associating it to another drug in the non-responding population.

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Funding: Labex Medalis, University of Strasbourg, France.

Disclosure: All authors have declared no conflicts of interest.

383P A phase I dose-escalation study of the novel peptide ALM201 in patients (pts) with advanced solid tumours

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Background: ALM201 is a novel 23-amino acid peptide derived from FKPB-L, a human endogenous protein with inherent anti-angiogenic activity. Pre-clinically, ALM201 potently inhibits cell migration, invasion and neo-vessel formation without effects on cell cycle or proliferation.

Methods: We enrolled pts with solid tumours using a single patient (10 - 40mg) then 3 + 3 (80 - 300mg) dose escalation design. ALM201 was administered subcutaneously (S.C.) once daily on days 1-5, 8-12, and 15-19 every 21 days. All pts continued until disease progression (PD) or dose-limiting toxicity (DLT). Primary objectives were to determine the safety, tolerability and recommended phase II dose (RP2D) of ALM201. Secondary objectives were to determine the pharmacokinetics (PK) and anti-tumour activity. Plasma and urine samples were analysed by a validated LC-MS/MS method.

Results: We report interim data in 18 evaluable pts enrolled in 8 dose levels. Cancers included ovarian (5), colorectal (4), NSCLC (2), endometrial (1), gallbladder (1), cervical (1), urachal (1), renal (1), pancreatic (1) and mesothelioma (1). Doses of 10 - 300mg were well tolerated. No DLTs were observed. The only toxicity was grade 1 injection site skin reaction. Median treatment duration was 11.1 weeks (range 3-18 wks). Two patients had stable disease for up to 6 cycles prior to progression. Maximal plasma concentrations were typically observed 1.5h (0.75-4h) after dosing indicating fairly rapid absorption. Above 40mg, plasma concentrations were consistently seen up to 6h after dosing (assay LLOQ = 100ng/mL). Where the terminal phase could be defined, half-lives <2h were reported (0.9-1.8h, n = 4 pts). Plasma C_{max} and AUC tended to increase with dose; with no evidence of dose non-proportionality between 10 - 160mg and lower than proportional increases in exposure observed above 160mg. No evidence of drug accumulation was observed over successive dose cycles. No unchanged parent drug was detectable in patient urine in the 0-6h collection phase after dosing.

Conclusions: Monotherapy ALM201 administered S.C. demonstrated a very good safety profile and acceptable PK in patients with advanced solid tumors. The RP2D analysis is currently ongoing.

Clinical trial identification: EudraCT No: 2014-001175-31

Legal entity responsible for the study: Almac Discovery

Funding: Almac Discovery and Invest Northern Ireland

Disclosure: R. Kennedy: Employee at Almac Diagnostics & Almac Group. A. Cranston: Employee at Almac Discovery. All other authors have declared no conflicts of interest.

385P Interim pharmacokinetic (PK) and pharmacodynamic (PD) data from the first-in-human study of NUC-3373, a pyrimidine nucleotide analogue, in patients with advanced solid tumors

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Background: NUC-3373, a phosphoramidate transformation of FUDR, is designed to bypass 5-FU and capecitabine resistance. Intracellular levels of the active 5-FU metabolite FUDR-MP in vitro were 363x higher than with 5-FU. Here, we report the interim PK and PD data from the ongoing first-in-human dose-escalation study of NUC-3373 in patients (pts) with advanced solid tumors (NuTide:301).

Methods: NUC-3373 was administered as 30- min IV infusion on days 1, 8, 15 and 22 of a 28-day cycle. The first 3 pt cohorts received NUC-3373 at 125mg/m^2, 250mg/m^2 and 500mg/m^2. The primary objective was to determine RP2D. Secondary objectives included safety, PK and PD profiles, and anti-tumour activity. Blood samples were collected pre-dose and at 11 time-points up to 48h post-dose during cycle 1. Plasma and intracellular metabolites were measured by UPLC-MS/MS; western blotting of extracted PBMCs measured thymidylate synthase (TS) within ternary complexes (TS-T).

Results: PK/PD analyses were conducted on 16 of the 17 pts recruited to the first 3 dosing cohorts pts (94%), median age 59 yrs (range 24-71), with 7 cancer types, the majority (76%) being colorectal cancer. Mean plasma Cmax and AUC of NUC-3373 were dose proportional. Linear PK was confirmed across the studied dose range with clearance of 3.4 ± 0.6 L/hr and plasma $t_{1/2}$ of 9.4h ±0.98h. Intracellular FUDR-MP was detectable at 5 minutes post-infusion with $t_{1/2}$ of 14.3h ±1.7h and was still present at 48h. In the 500mg/m^2 cohort the mean intracellular Cmax and AUC_{0-24} of FUDR-MP were 4.2pmol/10^6 cells and 16.5pmol/10^6 cells/hr. Within 1 hour of infusion, FUDR-MP was present within TS-T leading to depletion of the intracellular dTMP pool after 2-4h. Toxic metabolites FBAL and FUTP were undetectable intracellularly or in plasma. Dose escalation continues.

Conclusions: PK/PD data demonstrate NUC-3373 generates high intracellular concentrations of the active cytotoxic metabolite FUDR-MP, which efficiently sequester TS into TS-T inhibiting its activity. This and lack of toxic metabolite accumulation indicate NUC-3373 has a favorable PK profile compared to the established fluoropyrimidines.

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Legal entity responsible for the study: University of Oxford

Funding: Nucana BioMed Ltd

Disclosure: D.J. Harrison: Advisory in Cytosystems, Nucana and Ryboquin. Leadership role in Ryboquin The Institute received research funding from Nucana Ltd and Ryboquin Ltd. T.R.J. Evans: Advisory role in Bristol-Myers Squibb, Vertex, GSK, Baxter and Celgene. The institute received research funding from several Pharmaceutical companies. S.P. Blagden: Advisory role in Celgene and Novartis. Holder of an IP in RNA Guardian. Travel grant from Nucana. All other authors have declared no conflicts of interest.

386P Efficacy of pembrolizumab in phase 2 KEYNOTE-164 and KEYNOTE-158 studies of microsatellite instability high cancers

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Background: A high level of microsatellite instability (MSI-H) is indicative of a tumor deficient in mismatch repair (dMMR). Prior reports suggest that anti-PD-1 antibody therapy provides durable responses in patients (pts) with MSI-H cancers. Here we assessed efficacy of PD-1 blockade using pembrolizumab in pts with dMMR/MSI-H (hereafter termed MSI-H) advanced cancer enrolled in two ongoing, global, multicenter phase 2 studies KEYNOTE (KN)164 and KN158. We report results in 61 pts with MSI-H CRC and 77 pts with MSI-H non-CRC across 20 tumor types.

Methods: KN164 enrolled pts with MSI-H colorectal cancer (CRC) and ≥2 prior therapies, whereas the multicohort KN158 study included pts with MSI-H non-CRC and ≥1 prior therapy. MSI-H status was determined locally by IHC or PCR or centrally by PCR. Eligible pts in both studies received pembrolizumab 200 mg Q3W. Tumor response was assessed every 9 wk. Primary endpoint was ORR by independent central review per RECIST v1.1. Database cut-off date was Feb 10, 2017 for KN164 (≥54 wk follow-up) and Jan 27, 2017 for KN158 (≥27 wk follow-up).

Results: KN164 enrolled 61 pts with MSI-H CRC (90% with ≥2 prior therapies) and KN158 enrolled 77 pts with MSI-H non-CRC (52% with ≥2 prior therapies), at data cutoff. Tumor types represented in KN158 in at least 2 pts included endometrial (n = 17), gastric (n = 11), small intestinal (n = 10), pancreatic (n = 9), biliary (n = 8), mesothelioma and small cell lung (n = 3 each), adrenocortical, bladder, and thyroid (n = 2 each) cancers. ORR was 27.9% (n = 17 [all confirmed]; 95% CI 17.1%-40.8%) for MSI-H CRC and 37.7% (n = 29 [23 confirmed and 6 unconfirmed]; 95% CI 26.9%-49.4%) for MSI-H non-CRC. Median DOR was not reached for MSI-H CRC (range 2.9+ to 12.5+) or MSI-H non-CRC (range 2.4+ to 9.2+). Median OS was not reached for either MSI-H CRC or MSI-H non-CRC, with 6-mo OS rates of 87% and 73%, respectively.

6-mo PFS rates were 43% for MSI-H CRC and 45% for MSI-H non-CRC. 4 (7%) pts with MSI-H CRC and 7 (9%) with MSI-H non-CRC had serious drug-related AEs. The safety profile was consistent with that previously seen for pembrolizumab.

Conclusions: Pembrolizumab provides robust antitumor activity with durable responses in heavily pretreated pts with MSI-H cancers.

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387P Preliminary results from subsets of patients (pts) with advanced gastric cancer (GC) and esophageal carcinoma (EC) in a dose-escalation/expansion study of BGB-A317, an anti-PD-1 monoclonal antibody (mAb)

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Background: BGB-A317 is a humanized IgG4 anti-PD-1 mAb that blocks PD-L1/L2 binding to PD-1 restoring T-cell-mediated tumor inhibition. The Fc-hinge region has been engineered to preclude FcγR1-mediated binding to macrophages/myeloid-derived suppressor cells (MDSCs). Upregulation of PD-1/L1 and predominance of macrophages and MDSCs have been reported in GC and EC supporting the rationale of evaluating BGB-A317 in pts with GC or EC.

Methods: This ongoing, open-label, dose-escalation/expansion study is being conducted to evaluate the safety, tolerability and anti-tumor activity of BGB-A317 in pts with advanced solid tumors. Pts with histologically confirmed advanced GC or EC were eligible and treated with BGB-A317 at 2 mg/kg or 5 mg/kg every two weeks (Q2W) or Q3W. Adverse events (AEs) were assessed per NCI-CTCAE v4.03 and tumor assessments were performed approximately every two months via RECIST v1.1.

Results: As of 6 MAR 2017, 55 pts [median age 62 yrs (22-81)] with recurrent/refractory GC (n = 28) or EC (n = 27) were treated. Most were Caucasian (n = 36) and all pts had received ≥1 prior line of anti-cancer treatment. Median treatment duration was 51 days (5–363); 19 pts remain on study. The most common treatment-emergent AEs were fatigue (n = 11), nausea (n = 9) and dysphagia (n = 8); 46% pts experienced AEs ≥Grade (Gr) 3 but none were treatment related. One serious AE (diarrhea [Gr 2]) was considered related to treatment by investigators. Of the 47 evaluable pts, the disease control rate, defined as the proportion of pts who achieved complete or partial response (CR or PR) or stable disease (SD), is 32%. PRs have been reported in 3 pts (GC = 2; EC = 1) with duration of responses being 96, 125 and 188 days respectively, 2 pts are still on treatment; 5 initial documentations of PRs awaiting confirmation (GC, n = 2; EC, n = 3) have been reported in 12 pts with SD (GC = 5; EC = 7).

Conclusions: BGB-A317 appears to be generally well tolerated in pts with recurrent/refractory GC or EC. The preliminary safety profile and anti-tumor activity appear to be consistent with other checkpoint inhibitors and support continued exploration and development of BGB-A317 in pts with advanced GC or EC.

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Legal entity responsible for the study: Beigene Ltd.

Funding: Beigene Ltd.

Disclosure: J. Desai: Honoraria: Bayer, Merck Serono, Novartis. Consulting or advisory role: Amgen, Bayer, Bionomics, Circadian Technologies, Merck Serono, Norvartis. Research funding: GlaxoSmithKline (Inst), Roche-Genentech (Inst), Ventana Medical Systems (Inst). B. Markman: Personal fees from BeiGene during the conduct of the study. V. Atkinson: Honoraria: Bristol-Myers Squibb; MSD; Novartis. Consulting/advisory role: Bristol-Myers Squibb; MSD; Novartis. Travel, accommodations, expenses: Bristol-Myers Squibb; MSD; Novartis. A. Zhu: Research Funding: Lilly (Inst). J. Song: Employee of BeiGene USA, Inc. Q. Qi: Employee of Beigene (Beijing) Co. Ltd. A. Kang: BeiGene employee. All other authors have declared no conflicts of interest.

388P Preliminary results from a subset of patients (pts) with advanced head and neck squamous carcinoma (HNSCC) in a dose-escalation and dose-expansion study of BGB-A317, an anti-PD-1 monoclonal antibody (mAb)

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Background: BGB-A317 is a humanized IgG4 anti-PD-1 mAb that blocks PD-L1/PD-L2 binding to PD-1 restoring T-cell mediated tumor response. The Fc-hinge region has been engineered to preclude FcγR1 mediated binding to macrophages/myeloid-derived suppressor cells, a potential mechanism of PD-1 bound T-cell clearance. Regulatory $Foxp3^+$ T-cells and PD-1^+T-cell infiltration in the tumor microenvironment have been reported in HNSCC supporting the rationale for evaluation of BGB-A317 in pts with HNSCC. Here we present the preliminary results from a subset of pts with HNSCC treated with BGB-A317.

Methods: This ph 1, open-label, multi-center, dose-escalation/expansion study was conducted to evaluate the safety, tolerability, and anti-tumor activity of BGB-A317 in pts with advanced solid tumors. Pts with histologically confirmed advanced HNSCC who progressed following standard of care treatment were eligible to receive BGB-A317 administered at a dose of 5 mg/kg Q3W. Adverse events (AEs) were assessed per NCI-CTCAE v4.03. Tumor assessments were performed Q9W per RECIST v1.1.

Results: As of 6 Mar 2017, 18 pts with recurrent HNSCC were enrolled (median age, 63 years [25-78]). Most pts were male (89%), Caucasian (67%) and had received ≥2 prior lines of anti-cancer treatment. The median treatment duration for BGB-A316 was 104 days (30-245); 7 pts remain on study. Most treatment-emergent AEs were Grade (Gr) 1/2 in severity and the more common AEs were fatigue (n = 6), constipation (n = 3) and ear discomfort (n = 3). Eleven unique AEs ≥Gr 3 were reported in 7 pts: dysphagia, nausea salivary gland enlargement, dyspnea, pleuritic pain, aspiration pneumonia,

infection-related COPD exacerbation, parotitis, ocular hyperemia, and wound hemorrhage. A partial response (PR) has been confirmed in 1 pt, and 8 pts have stable disease (SD,) including 2 unconfirmed PRs. The disease control rate, defined as the proportion of pts who have achieved CR, PR and SD, is 50%.

Conclusions: BGB-A317 appears to be well tolerated in pts with recurrent HNSCC. The preliminary safety profile and anti-tumor activity support continued investigation of BGB-A317 in this setting.

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Disclosure: L. Horvath: Clinical trials agreement with budget from Beigene, during the conduct of the study; J. Desai, S. Sandhu: Honoraria: Bayer, Merck Serono, Novartis. Consulting or advisory role: Amgen, Bayer, Bionomics, Circadian Technologies, Merck Serono, Norvartis. Research funding: GlaxoSmithKline (Inst), Roche-Genentech (Inst), Ventana Medical Systems (Inst). A.G. Hill: Research funding, Stock and Other Ownership Interests: Tasman Oncology. Travel Accommodations, Expenses: Bristol-Myers Squibb. B. Markman: Personal fees from Beigene during the conduct of the study. Z. Chen, J. Hou: Employee of BeiGene Ltd. X. Tan: Employee of BeiGene (Beijing) Co. Ltd. All other authors have declared no conflicts of interest.

389P Preliminary results from a subset of patients (pts) with advanced ovarian cancer (OC) in a dose-escalation/expansion study of BGB-A317, an anti-PD-1 monoclonal antibody (mAb)

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Background: BGB-A317 is a humanized IgG4 anti-PD-1 mAb that blocks PD-L1/L2 binding to PD-1 restoring T-cell-mediated tumor inhibition. The Fc-hinge region has been engineered to preclude FcγR1 mediated binding to macrophages/myeloid-derived suppressor cells (MDSCs). Upregulation of PD-1/L1 and predominance of macrophages and MDSCs have been reported in OC supporting the rationale of evaluating BGB-A317 in pts with OC.

Methods: An open-label, multi-center, dose-escalation/expansion study is being conducted to evaluate the safety, tolerability and anti-tumor activity of BGB-A317 in pts with advanced solid tumors. Pts with histologically confirmed advanced OC were eligible and treated at different dose levels (0.5, 2, 5, 10 mg/kg intravenously [IV] every 2 weeks [Q2W] in dose escalation, or at 2 or 5 mg/kg IV Q2W or Q3W, or 200 mg IV Q3W in dose expansion, or 5 mg/kg IV Q3W in indication expansion). Tumor assessments, including CA125, occurred approximately every 2 months and response was collected according to both RECIST 1.1 and GCIG criteria. Adverse events (AEs) were assessed per NCI-CTCAE v4.03.

Results: As of 6 Mar 2017, 51 pts [median age 62 (19–80) yrs] with recurrent/refractory OC were enrolled. Most pts were Caucasian (88%), all had received ≥1 prior line of anti-cancer treatment (median 3 [1–12]). Median duration of treatment was 68 (22–446) days; 7 pts remain on study. The most common treatment-emergent AEs were nausea (37%), fatigue (28%), and abdominal pain (28%). 49% of pts experienced an AE ≥Grade (Gr) 3; stomatitis (n = 1) and diarrhoea (n = 1) were Gr 3 AEs considered treatment-related by investigators. Mucosal inflammation, pyrexia and colitis were serious AEs considered treatment-related by investigators (n = 1, each). Among 51 evaluable pts, the disease control rate is 43%; 2 PRs have been reported including 1 pt who remains on study and to date has achieved an 89% reduction in target lesions.

Conclusions: BGB-A317 appears to be generally well tolerated in pts with recurrent/refractory OC. The preliminary safety profile and anti-tumor activity are consistent with that observed with other checkpoint inhibitors and support continued investigation of BGB-A317.

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Funding: Beigene Ltd

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390P A phase I study of durvalumab (D) in combination with olaparib (O) and cediranib (C) in recurrent women's cancers

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Background: Recent data showed a PARP inhibitor, O and a VEGFR1-3 inhibitor, C together are clinically superior to O alone in recurrent platinum-sensitive ovarian cancer (OvCa). We hypothesized reduced VEGF signaling by C and DNA damage by O may complement anti-tumor activity of immune checkpoint blockade, D. We previously reported the safety data and RP2D of D in combination with O or C. We now report RP2D and PK/PD data of the D+O+C therapy (NCT02484404).

Methods: Eligible patients (pts) with PS 0-1 and good end organ function received D+O+C in a 3 + 3 design. An intermittent C schedule (C; 5 days on/2 days off) at 15 or 20 mg (dose level: 1, 2) was combined with D 1500 mg IV q28 days, and O tablets 300 mg BID. The DLT period was one 28d cycle. Safety was assessed by CTCAEv4.0 and response by RECISTv1.1. Plasma samples were collected for O and C PK analysis and for pro-inflammatory cytokines (IFN-γ, IL-10, IL-12, IL-2, IL-6, IL-8 and TNF-a) pre-treatment and on therapy (cycle 1 day 15 and cycle 3 day 1).

Results: Nine women (median age 59yr [44-73], and median 3 prior therapies [2-6]) were treated. Of the 9 pts, 7 had OvCa, 1 endometrial (EnCa) and 1 triple negative breast Ca. Grade 3/4 AEs include hypertension (1/9), anemia (1/9) and lymphopenia (3/9). No pts experienced DLTs. One patient required dose reduction during cycle 5, for grade 3 anemia. Three PRs were observed in 2 OvCa and 1 EnCa (response rate of 33%, median 5 months [4^+-6^+]), and 4 had SD (median 5 months [3^+-10^+]), yielding 78% disease control rate. There were no significant changes in O and C PK parameters caused by D and the co-administration of C or O. All cytokines plasma levels were not changed significantly by the treatment. PD-L1 expression by IHC and immune subsets by flow cytometry are under analysis.

Conclusions: The RP2D for D+O+C (D 1500 mg q28d+O 300 mg tablets BID+C 20 mg 5 days on/2 days off) is tolerable and active in recurrent women's cancers. A phase II expansion study of D+O+C is to open in OvCa.

Clinical trial identification: (NCT02484404)

Legal entity responsible for the study: National Cancer Institute Center for Cancer Research

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Disclosure: All authors have declared no conflicts of interest.

391P Phase I expansion of olaparib (PARP inhibitor) and AZD5363 (AKT inhibitor) in recurrent ovarian, endometrial and triple negative breast cancer

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Background: We sought to confirm the recommended phase II dose (RP2D) of the combination of olaparib and AZD5363 in women's cancers and evaluate molecular markers of response and resistance.

Methods: Olaparib tablet formulation (O) was given orally BID, AZD5363 (A) was given orally on a 4 day on/3 day off schedule. Two dose levels were planned per the ComPAKT study (Yap AACR 2015). Responses were defined using RECIST 1.1.

Patients had biopsies at baseline and after 28 days of treatment for planned correlative testing.

Results: To date, 38 patients (pts) have been enrolled. Median number of prior therapies was 4 (1-8). Only 7 (18%, 5 ovarian, 2 breast) pts had known germline BRCA mutation. The first two pts on DL1 (O 300mg; A 400mg) experienced DLTs of diarrhea and vomiting. Therefore, 6 pts were treated on DL-1 (O 300mg; A 320mg). There were no DLTs on DL-1, therefore, 6 additional pts were treated on DL1. There were no DLTs on re-explored DL1. DL1 was confirmed as the RP2D. Expansion phase was performed with an additional 24 pts. Most common adverse events (≥15%) were anemia (89%, G3/4 16%), nausea (76%, G3/4 5%), diarrhea (74%, G3/4 5%), leukopenia (61%, G3/4 11%), elevated creatinine (58%, G3/4 3%), hyperglycemia (42%, G3/4 0%), fatigue (42%, G3/4 0%),vomiting (39%, G3/4 5%), anorexia (32%, G3/4 0%), mucositis (26%, G3/4 0%), hypertriglyceridemia (18%, G3/4 0%), thrombocytopenia (18%, G3/4 0%), neutropenia (18%, G3/4 10%), hypercholesterolemia (18%, G3/4 0%), hyponatremia (16%, G3/4 5%) and constipation (16%, G3/4 0%). Of 30 pts evaluable for response, overall response rate (RR) was 24%. Seven had confirmed partial response including 1 ovarian, 4 endometrial and 2 triple negative breast cancer pts. RR among endometrial cancer pts was 50% (4/8). Six additional pts had stable disease for greater than 4 months including 4 ovarian and 1 endometrial cancer pts. Assessment of molecular correlatives of response and resistance are ongoing.

Conclusions: The combination of olaparib tablet formulation and AZD5363 is well tolerated at the confirmed RP2D and demonstrates preliminary evidence of durable tumor activity in ovarian, endometrial and triple negative breast cancer. Promising response was seen in the endometrial cancer cohort.

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Legal entity responsible for the study: University of Texas MD Anderson Cancer Center

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392P Generation of a novel preclinical PK/PD model provides insights into PARP inhibitor clinical monotherapy activity

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Background: In Phase II trials, an olaparib capsule dose that inhibits PARP (100 mg bd) was clinically inferior to the MTD (400 mg bd). Using an in vivo model, we investigated this discrepancy and the effect of dose and schedule on tumour progression.

Methods: PK, PD and antitumour activity were assessed using olaparib (100, 50, 25, 10, 2.5 mg/kg qd) in a breast cancer patient-derived xenograft (PDX) with mutated BRCA2 and TP53. We studied the relationship between PARP1 inhibition and DNA single-strand breaks (SSBs) by creating a mathematical model. We also compared PK/PD model parameters with free minimum olaparib steady-state plasma concentration ($C_{min,ss}$) in seven Phase I–III clinical studies.

Results: Only 100 and 50 mg/kg olaparib doses caused tumour regression, yet all but the lowest led to acute PAR inhibition. The differentiating factor was time over PAR IC_{95}; simulations using the mathematical model at steady state predicted a threshold where >95% reduction in PAR caused >20-fold increase in DNA SSBs. Overlaying clinical data, we saw that 400 mg bd capsule and 300 mg bd tablet doses provide continuous PAR inhibition ($C_{min,ss}$>IC_{95} upper confidence level); 100 mg bd capsule does not. Dosing schedule assessment showed PDX regression with continuous 100 mg/kg olaparib (0/10 tumours progressed by day 100). By contrast, continuous dosing at 50 mg/kg or intermittent dosing (1 wk on/1 wk off) at 100 mg/kg resulted in 2/10 and 10/10 progressions, respectively. Treatment withdrawal upon regression led to regrowth in all cases; re-challenge at continuous 100 mg/kg was effective (9/10 regressions), 50 mg/kg was not (0/10). In a maintenance setting, switching to lower or intermittent dosing resulted in tumour response more similar to that of continuous 100 mg/kg (1/10, 2/10 and 0/10 progressions, respectively).

Conclusions: Discrepancy between biologically and clinically effective olaparib doses is explained by a need for continuous >95% PAR inhibition. Both the 400 mg bd capsule and 300 mg bd tablet dose, used in the ongoing clinical programme, provide this. Dosing schedule data suggest continuous PAR inhibition is also needed for long-term responses. These data highlight important principles for treatment of patients with PARP inhibitor monotherapy.

Legal entity responsible for the study: AstraZeneca

Funding: AstraZeneca

Disclosure: M. O'Connor, E. Cadogan, A. Hughes, M. Learoyd, H. Xu, J. Li, J. Yates: Employee of AstraZeneca and owns stock with AstraZeneca. E. Leo: Employee of AstraZeneca.

393P Pharmacodynamic (PD) biomarkers for the p70S6K/Akt inhibitor, M2698: Translation from animal to human and relevance to dose selection

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Background: M2698 is an oral, potent and selective inhibitor of p70S6K/Akt1/3 in the PAM pathway with the potential to block signaling from the Akt feedback loop and overcome tumor resistance. Preclinical studies suggest a steep exposure – adverse event relationship. Therefore, insights into drug-dependent target modulation (S6 phosphorylation (pS6) inhibition) and its association with efficacy could inform dose selection.

Methods: Pharmacokinetic (PK) data from the phase I, first-in-human (FIH) dose escalation trial conducted in patients with advanced cancer who received daily (d) oral M2698 (15-320mg/d) were evaluated by nonlinear, mixed effect modeling. Using a PK/PD model developed with data from a breast tumor cell line derived xenograft (CLDX) in mice, tumor pS6 time profiles in humans were simulated using a mouse PD model driven by human PK. Model predictions were calibrated by comparing simulations to clinical observations, with an assumed variation in sensitivity (IC_{50}) to pS6 between CLDX and human tumors. Predicted pS6 time profiles and clinically observed pS6 inhibition in human tumors and peripheral blood mononuclear cells (PBMC) informed the dose escalation decision in the FIH study.

Results: M2698 PK profiles were best described by a two-compartment linear model with transit compartments for delayed absorption. Consistent exposure-dependent effects of pS6 inhibition in PBMCs were observed at 160-320 mg/d, with 70-80% pS6 inhibition observed in some tumors. Based on predicted pS6 inhibition, CLDX tumors were 2-3x more sensitive than human tumors. Applying a 2-3x higher IC_{50}, simulations suggested that 250-350mg/d would achieve the PD threshold of continuous tumor pS6 inhibition ≥ 80% in 90% of a human population, leading to escalation to 380mg/d.

Conclusions: Understanding inter-species variation can improve the precision of preclinical-to-clinical translation. For M2698, preliminary clinical PD data showed that human tumors were 2-3x less sensitive to pS6 inhibition than CLDX tumors in mice. Collective PMBC and tumor PD outcomes suggest that 160 -320 mg/d M2698 may result in considerable pS6 inhibition; a range for selection of a phase 2 dose.

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Legal entity responsible for the study: Merck KGaA

Funding: Merck KGaA

Disclosure: W. Xiong, I. Celik, P. Girard: Merck employee. H. Tian, A. Clark, J. Shaw, R. Kaleta: EMD Serono employee

394P Phase 1 study of ipatasertib (AKT inhibitor) for investigating safety, tolerability, pharmacokinetics (PK), efficacy, and biomarkers in Japanese patients (pts) with solid tumors including castration-resistant prostate cancer (CRPC)

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Background: Ipatasertib is a highly selective small-molecule inhibitor of AKT showing antitumor activity. Clinical efficacy and safety in non-Japanese pts with metastatic

CRPC has been reported (ASCO, ESMO 2016). We investigated safety, tolerability, PK, efficacy, and biomarkers in Japanese pts.

Methods: Phase 1, open label, dose-escalation study; 3 + 3 design. Primary endpoints were safety, tolerability, and PK. In Stage 1, pts with solid tumors were administered 200, 400, or 600 mg ipatasertib PO daily for 21 days of a 28-day cycle. In Stage 2, pts with CRPC were administered ipatasertib (200 or 400 mg PO daily) in combination with abiraterone acetate (AA) (1000 mg PO daily) plus prednisolone (5 mg PO twice a day) for the whole 28-day cycle. In an exploratory analysis of biomarkers, we investigated the relationship between PI3K pathway alterations (PIK3CA mutation or amplification and PTEN loss) and clinical efficacy of ipatasertib.

Results: A total of 21 pts were enrolled. Stage 1: 3, 4, and 8 pts were enrolled in the 200, 400, and 600 mg cohorts. One pt in the 600 mg cohort experienced DLT [Gr3 nausea]. The most common AEs of any grade (≥30% of pts) were nausea, diarrhea, decreased appetite, vomiting, and fatigue. C_{max} and AUC of ipatasertib were dose-proportional from 200 to 600 mg. Eight pts had stable disease (SD); 2 of those 8 pts continued study treatment beyond 4 months. Stage 2: 3 pts each were enrolled in the 200 and 400 mg cohorts. No DLTs were observed. The most common AEs of any grade were nausea, diarrhea, vomiting, diabetes mellitus, dysgeusia, and dizziness. Ipatasertib C_{max} and AUC were similar to those in monotherapy. Of the 6 pts, complete response was observed in 1 pt and SD was observed in 1 pt. Three pts continued study treatment beyond 4 months; 2 of those 3 pts had previously received AA and enzalutamide. Biomarker results will be presented.

Conclusions: Ipatasertib was well tolerable for Japanese pts. Based on our results, the recommended doses of ipatasertib for further development are 600 mg for monotherapy and 400 mg for in combination with AA plus prednisolone.

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Legal entity responsible for the study: Chugai Pharmaceutical co., LTD.

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395P DS-1205b, a novel, selective, small-molecule inhibitor of AXL, delays the onset of resistance and overcomes acquired resistance to EGFR-TKIs in a human EGFR-mutant NSCLC (T790M-negative) xenograft model

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Background: AXL is a receptor tyrosine kinase that plays an important role in signal transduction in normal and malignant cells. Abnormal expression and/or activation of AXL can provide a survival advantage for certain cancer cells, and AXL up-regulation is associated with poor prognosis in several cancers. Recently, it has been reported that up-regulation of AXL expression is a mechanism of EGFR-TKI resistance in EGFR-mutant non-small cell lung cancer.

Methods: Kinase activity was measured by mobility shift assay. The inhibition of hGAS6-induced migration was measured in AXL-transfected NIH3T3 (NIH3T3-AXL) cells. The in vivo anti-tumor effects of DS-1205b mono- and combination-therapy with EGFR-TKI were evaluated in NIH3T3-AXL allograft and HCC827 xenograft models. Protein expression was analyzed by Western blot or immunohistochemistry and gene expression was analyzed by RT-PCR or RNA seq.

Results: We found that DS-1205b selectively inhibited AXL kinase activity with IC_{50} of 1.3 nM, and with NIH3T3-AXL cells, DS-1205b potently inhibited the hGAS6-induced migration in vitro with EC_{50} of 2.7 nM. DS-1205b monotherapy exerted significant antitumor activity in an NIH3T3-AXL allograft model. In an HCC827 xenograft model, combination treatment with DS-1205b and osimertinib significantly delayed on the onset of tumor resistance compared to osimertinib alone in a manner proportional to DS-1205b does. DS-1205b also showed a similar resistance delay effect with erlotinib combination in the same xenograft model. AXL up-regulation was associated with the development of resistance to erlotinib treatment in another HCC827 xenograft study, and DS-1205b restored the antitumor activity of erlotinib in erlotinib-resistant tumors in a dose-dependent manner.

Conclusions: In an HCC827 xenograft model of EGFR-mutant NSCLC, inhibition of AXL activity by DS-1205b restored sensitivity to erlotinib, and addition of DS-1205b to osimertinib delayed the onset of resistance to osimertinib. These findings support further non-clinical and clinical studies targeting inhibition of AXL in EGFRm NSCLC.

Legal entity responsible for the study: Daiichi Sankyo Co., Ltd.

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Disclosure: T. Jimbo, T. Taira, T. Komatsu, K. Kumazawa, N. Maeda, N. Haginoya, T. Suzuki, M. Ota, Y. Totoki, C. Wada, K. Inaki, T. Isoyama, M. Uno: All authors are employees of Daiichi Sankyo Group which is developing DS-1205c.

397P Immune related adverse events (irAEs) in early phase immunotherapy (IO) trials: Implications for recommended phase 2 dose (RP2D) determination

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Background: IO agents have a unique profile of irAEs. Due to the potential of delayed severe irAEs, we examined if conventional dose-limiting toxicity (DLT) periods may underestimate the rate of clinically significant irAE (csAE), defined as an irAE that required systemic therapy, drug delay or discontinuation.

Methods: A retrospective chart review of patients (pts) on early phase IO trials at Princess Margaret Cancer Centre examined severity (CTCAE v4.0), management, timing of onset and resolution of all grade (G) irAEs. A generalized estimating equation model assessed the association between time on treatment (Rx) and csAE, adjusted for duration of IO. Potential predictors of csAEs were assessed.

Results: From 8/2012-9/2016, 239 pts across 21 trials received ≥1 dose of IO (72% single agent; 28% IO-based combination). The most common tumors were melanoma (23%) and lung (18%) cancer. Among 890 total Rx-related irAEs, 93 (10%) were csAEs, including 22 (24%) endocrine, 15 (16%) gastrointestinal [GI], 11 (12%) respiratory, 10 (11%) skin and 9 (10%) hepatic csAEs. Median onset was ≤90 days for hepatic, GI and general (eg fatigue) csAEs, and >90 days for endocrine, respiratory, skin and musculoskeletal csAEs ($P = 0.03$). One pt with G3 hepatitis and G4 hypophosphatemia met protocol-defined DLT criteria and 27 irAEs fulfilled DLT criteria but occurred after the DLT period. 61 pts had csAEs, with 21 (34%) having >1 csAE. The onset of first csAE was 0-6 weeks (wks) in 30 (49%) pts; wks 7-12 in 16 (26%); wks 13-48 in 10 (16%); and ≥49 wks in 5 (8%) pts. The odds ratio (OR) for the first csAE occurrence within first 6 wks vs ≥ 6 wks was 3.3 (95% CI 2.0-5.6, $P = 0.002$), accounting for varying Rx duration. After adjustment for time on Rx, csAE correlated only with response on univariate analysis (OR 4.3, 95% CI 2.1-8.9, $P < 0.001$), but not with single or combination IO, age, ECOG status, prior IO or prior therapy lines.

Conclusions: Risk of first-onset csAE was higher during the initial 6 wks of IO, supporting use of conventional DLT period for dose escalation decision. However, as late csAEs were also seen, RP2D determination should consider the entire temporal course of csAE. Occurrence of csAEs positively correlated with response to IO, relative to time on Rx.

Legal entity responsible for the study: Princess Margaret Cancer Centre

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398P Drug-induced electrolyte abnormalities in oncology phase I trials: Analysis of 1088 cases treated at The Royal Marsden Hospital

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Background: The incidence and clinical significance of electrolyte abnormalities (EAs) in phase I studies is not well documented. The objective of this study is to evaluate the incidence of EAs, graded according to CTCAE v4.03, and its correlation with factors influencing them.

Methods: A retrospective chart review was performed of 1088 cases in 82 phase 1 clinical trials consecutively treated from 2011 to 2015 at the Drug Development Unit, The Royal Marsden Hospital. Cox regression was used to examine the relationship between overall survival and baseline characteristics, treating the occurrence of grade 3/4 EAs as a time-varying covariate.

Results: The most common EAs in all grades during trials are: hyponatremia 62%, hypokalemia 40%, hypophosphatemia 32%, hypomagnesemia 17% and hypocalcemia 12%. Overall, grade 3/4 EAs occurred in 19% of cases. More specifically, grade 3/4 EAs were observed, as follow: hyponatremia 10%, hypophosphatemia 6%, hypokalemia 5%, hypomagnesemia 1%, hypermagnesemia 1%. Grade 3/4 EAs occurred during the dose-limiting toxicity window in 8.73% of cases. Overall, diarrhea was associated with hypomagnesemia in all grades (HR 1.78, 95% CI: 1.32-2.39, $p < 0.001$), with G3/G4 hypokalemia (HR 1.93, 95% CI: 1.09-3.43, $p = 0.02$) and hyponatremia in all grades (HR 0.79, 95% CI: 0.67-0.93, $p = 0.006$). Vomiting was also associated with hypomagnesemia in all grades (HR 1.45, 95% CI: 1.08-1.95, $p = 0.01$) and G3/4 hypokalemia (HR 2.91, 95% CI: 1.62-5.23, $p < 0.001$). Baseline hypoalbuminemia, hyponatremia and female gender are associated with higher risk of developing other EAs during trial in the univariate analysis. Patients who developed G3/4 EAs during follow-up had a poorer median overall survival (OS) (26 weeks vs 37 weeks, HR = 1.61; 95% CI: 1.37-1.90; $p < 0.001$).

Conclusions: Baseline EAs are common in patients with advanced cancers participating in phase I trials. This is the first study to demonstrate the clinical significance of baseline hypoalbuminemia and hyponatremia, which are predictors of development of other EAs in phase 1 patients. G3/4 EAs are adverse prognostic factors of OS independent of serum albumin levels.

Legal entity responsible for the study: The Royal Marsden Hospital NHS Foundation Trust

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400P LCZ 696, administered during doxorubicin, trastuzumab or pertuzumab treatment, prevents cardiotoxicity in our in vitro model

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Background: Doxorubicin (DX), Trastuzumab (T) and Pertuzumab (P) are antineoplastic drugs used in the treatment of breast cancer. Adverse cardiovascular events related to anticancer drugs are among the leading causes of morbidity and mortality in cancer patients. Sacubitril-valsartan (LCZ 696) is a combination drug, made up of neprilysin inhibitor sacubitril and angiotensin II receptor blocker valsartan, used for the treatment of heart failure in patients with a reduced ejection fraction. Here, we aim to assess whether LCZ 696, administered during DX, T or P treatment, reduces *in vitro* anticancer drugs-related cardiotoxicity compared to Valsartan (V), used as a control drug.

Methods: The H9C2 rat cardiomyoblasts were seeded in 96-well plates at a density of 1 x 10^4 cells/well and incubated at 37 °C with 5% CO2 for 16 hours. After the addition of 200 nM of T, P or DX in the culture medium, cells were incubated for 72 hours. The cells were further treated in the absence or presence of 10 μM of LCZ 696 or V for additional 3 days. Viable cells were counted by trypan blue exclusion test and cell survival was expressed as percentage of viable cells compared to control untreated cells.

Results: LCZ 696 reduced significantly T, P and DX related toxicity in H9C2 cardiomyoblasts as evidenced by the higher percentage of viable cells treated with combinations of T, P or DX with LCZ 696 with respect to cells treated with T, P or DX alone ($p < 0.001$). V reduced significantly T and DX related toxicity in H9C2 cardiomyoblasts treated with combinations of T or DX and V with respect to the cells treated with T or DX, used as single agents ($p < 0.001$). However there was no significant reduction of toxicity when H9C2 cells were treated with P + V. Thus, both LCZ 696 and V reduced significantly DX and T related toxicity when administered to H9C2 cardiomyoblasts after the antineoplastic treatment (no significant difference between LCZ 696 and V treatment, $p = 0.6$). Moreover, LCZ 696 was significantly more effective than V ($p < 0.001$) in reducing both T and P related toxicity when administered to cultures of H9C2 cardiomyoblasts after antineoplastic treatments.

Conclusions: LCZ 696, administered during DX, T or P treatment, significantly increases the viability of treated cells, thus reducing cardiotoxic effects of these drugs, as demonstrated by our *in vitro* experiments. The future perspective aims to test LCZ 696 in *in vivo* models to assess its capability to blunt left ventricular dysfunction after antineoplastic treatments.

Legal entity responsible for the study: Nicola Maurea

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Disclosure: M. De Laurentiis: Advisory Board: Novartis, Roche, Pfizer, AstraZeneca, Celgene, Eisai. All other authors have declared no conflicts of interest.

401P MEK inhibitor retinopathy

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Background: To evaluate the presence and characteristics of subretinal fluid (SRF) associated with the use of MEK inhibitors in the treatment of systemic cancer MEK retinopathy is described as symmetrical bilateral disease that develops in a time-dependent and dose-dependent manner.

Methods: In this prospective, observational study, collected data from 14 patients with locally advanced or metastatic cancer undergoing treatment with the MEK inhibitor as clinical trials between 2010-2013. They underwent regular ophthalmological examinations including determination of visual function, biomicroscopy, dilated fundoscopy and optical coherence tomography (OCT).

Results: Of the 14 participants, 10 (71%) were men; the mean (SD) age was 65 years (range, 41-80 years). Six (48%) study participants developed SRF during the study period. OCT revealed subfoveal neuroretinal elevation, serous retinal detachments often asymptomatic. In general it solves spontaneously without any apparent functional deficits or changes in structural integrity, and does not require the suspension of the treatment.

Conclusions: The presence of serous retinal detachment in patients undergoing treatment with the MEK inhibitor is common. Visual symptoms were mild and mainly transient and the presence of SRF did not lead to permanent ocular disorder. It is important to investigate all previous ocular disorders and pharmacologic interactions of MEK inhibitor that could associate with ocular effects.

Legal entity responsible for the study: START Madrid

Funding: None

Disclosure: All authors have declared no conflicts of interest.

402P A Phase I/II study everolimus in combination with paclitaxel-carboplatin in patients with advanced adenocarcinoma of the stomach

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Background: Significant proportion of patients (pts) with adenocarcinoma of stomach (ADCS) present with advanced disease. Paclitaxel (P), either alone, or in combination with carboplatin (C) is well-tolerated, but has modest activity in ADCS. The PI3K-Akt pathway played an important role in cell proliferation and apoptosis in pre-clinical ADCS models. Everolimus (E) is a potent inhibitor of mTOR, a downstream mediator of the PI3K-Akt pathway. Combining chemotherapies with mTOR inhibition may improve outcome

Methods: A single-arm, dose-escalation study of E, in combination with P and C (E+PC) was conducted in pts with metastatic and/or loco-regionally advanced ADCS [NCT01514110]. In the phase 1 portion (P1P), the maximum-tolerated dose (MTD), recommended phase 2 dose (RP2D) and safety of E+PC, were determined using a

standard 3 + 3 design. Starting dose (dose level I) was E 5mg/d, P 175mg/m^2 and C AUC5 every 3 weeks. Dose-limiting toxicities (DLT) were defined as grade 4 haematological or grade 3 or 4 non-haematological toxicities. Preliminary efficacy of E+PC in pts with ADCS, defined by clinical benefit rate (CBR) (CR+PR+SD for 6wks or more as per RECIST), and survival were determined in the phase 2 portion

Results: 30 pts were enrolled (P1P = 12) from Jan 2008 to Nov 2014. In the P1P, 2 DLTs (G5 GI bleeding and G3 joint pain) were experienced at dose level II, thus establishing dose level I as the MTD and RP2D. 21 pts were treated at RP2D. Baseline demographics of phase 2 portion: M/F: 9/12, Median age 54 (range 40-69), ECOG PS 0/1/2: 10/10/1. Prior lines of chemotherapy 0/1/≥2: 7/12/2. Median cycles: 6 (range 1-19). Common related ≥G3 adverse events (AEs) include (%): neutropenia (48%), anaemia (43%), thrombocytopenia (29%), mucositis (10%). Febrile neutropenia occurred in 10% (n = 2) of pts. 18 pts were evaluable for response (5 PR, 9 SD, 4 PD). CBR 77.8% (95% CI 58.6-97.0%). Median PFS and OS was 6.9 and 9.0months (95%CI 3.5 – 7.6; 3.8 – 15.1months) respectively

Conclusions: E+PC administered at RP2D was well-tolerated. Comparing with prior reported series of PC alone, E+PC showed more favorable efficacy and has promising activity in pts with advanced ADCS. Acknowledgement- Supported by Novartis Pharmaceuticals Ltd

Clinical trial identification: NCT01514110

Legal entity responsible for the study: The Chinese University of Hong Kong

Funding: Novartis Pharmaceuticals Ltd.

Disclosure: H.H. Loong: Research Funding: MSD. Advisory: Novartis, Roche. Travel Support: Abbvie, Bayer, Bristol-Myers-Squibb, Novartis, Roche. Speakers Bureau: Abbvie, Bayer. W. Yeo: Advisor: Novartis, Eli Lilly. All other authors have declared no conflicts of interest.

403P Phase I studies of the novel carcinoembryonic antigen T-cell bispecific (CEA-CD3 TCB) antibody as a single agent and in combination with atezolizumab: Preliminary efficacy and safety in patients (pts) with metastatic colorectal cancer (mCRC)

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Background: CEA-CD3 TCB (RG7802, RO6958688) is a novel T-cell bispecific antibody targeting CEA on tumor cells and CD3 on T cells. Preclinically, CEA-CD3 TCB had potent antitumor activity, leading to increased intratumoral T-cell infiltration and activation, T-cell–mediated tumor cell killing and PD-L1/PD-1 upregulation.

Methods: In 2 ongoing dose-escalation phase I studies, CEA-CD3 TCB is given as monotherapy IV QW (S1) or in combination (QW) with atezolizumab 1200 mg Q3W (S2) in pts with advanced CEA positive (> 20% of tumor cells expressing moderate or high) solid tumors. In S1, 80 pts (70 CRC) were treated at dose levels of 0.05-600 mg; in S2, 45 pts (35 CRC) at 5-160 mg.

Results: At doses ≥ 60 mg (31 evaluable pts with CRC in S1; 14 in S2), CT scans revealed signs of tumor inflammation within 48 h of the first dose, consistent with CEA-CD3 TCB mode of action. 2 (6%) CRC pts in S1 (both microsatellite stable [MSS]) and 3 (21.5%) in S2 (2 MSS CRC, 1 MSI high [out of 2]) had confirmed partial response (PR; RECIST v1.1). Additionally, tumor reduction of − 10% to − 30% (stable disease) was seen in MSS CRC pts (4 [13%] in S1 and 5 [36%] in S2). At weeks 4-6, 9 (29%) CRC pts in S1 and 7 (50%) in S2 had metabolic PR (FDG PET; EORTC criteria). At all doses in S1, the most common related AEs were pyrexia (56%), infusion-related reactions (IRRs; 50%) and diarrhea (40%). In S1 (out of 59 pts > 40 mg), the most common grade ≥ 3 (G3) related AEs were IRRs (24%) and diarrhea (7%). Five pts experienced DLTs: G3 dyspnea, G3 diarrhea, G3 hypoxia, G4 colitis and G5 respiratory failure (G4 and G5 at 600 mg [exceeding MTD]). DLT events were likely associated with tumor lesion inflammation, per investigators. In S2, there was no evidence of new or additive toxicities, with 2 DLTs at 160 mg (1 G3 ALT increase in a pt with liver metastases and 1 G3 maculopapular rash). Updated data will be presented.

Conclusions: Evidence of antitumor activity in advanced CRC and other CEA-expressing tumors was observed during dose escalation with CEA-CD3 TCB monotherapy. Enhanced activity and a manageable safety profile was seen in combination with atezolizumab.

Clinical trial identification: NCT02324257

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

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404P Dose escalation study of vemurafenib with crizotinib or sorafenib in patient with BRAF-mutated advance cancers

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Background: BRAF inhibitors are effective in melanoma and other cancers with *BRAF* mutations; however, patients ultimately develop therapeutic resistance through activation of alternative signaling pathways such as MET, PDGFR and CRAF. We hypothesized that combining the BRAF inhibitor vemurafenib and MET inhibitor crizotinib or PDGFR/CRAF inhibitor sorafenib can overcome resistance.

Methods: We designed a phase I study (3 + 3 design) to determine the safety of vemurafenib (240-960 mg PO BID q 28 days) with crizotinib (250 mg PO daily or BID q 28 days) in arm A or sorafenib (200 mg PO daily to 400mg PO BID q 28 days) in Arm B in patients with *BRAF*-mutant advanced cancers. Endpoints included maximum tolerated dose (MTD), dose limiting toxicities (DLT), safety, response (RECIST 1.1) and plasma cell-free DNA mutation analysis.

Results: Thirty-six patients (arm A, 13; arm B, 23), median number of 3 prior therapies (29 [81%] had prior BRAF/MEK inhibitors) were treated. Patients (melanoma 17/36, 47%; papillary thyroid cancer 5/36, 14%; colorectal cancer 3/36, 8%; lung adenocarcinoma 2/36, 6%; other 9/36, 25%) had *BRAF* V600E (30), V600K (3) or other *BRAF* mutations (3). Vemurafenib 720mg BID with crizotinib 250mg daily and vemurafenib 720 mg BID with sorafenib 400mg/200mg were identified as MTDs. DLTs included grade (G) 3 rash (2) in arm A and G3 rash and G3 hypertension in arm B. Other G3 treatment related toxicities were G3 fatigue (2), G3 anemia (1), G3 thrombocytopenia (1), G3 neutropenia (1), G3 thromboembolic event (1) in arm A and G3 hypertension (1), G3 headache (1), G3 diarrhea (2), G3 intraocular inflammation (1) in arm B. In Arm A, 3 of 13 (23%) patients (melanoma refractory to BRAF monotherapy [2] and

lung adenocarcinoma) attained a partial response (PR). In Arm B, 4 of 23 (17%) patients (ovarian cancer refractory to MEK inhibitor, melanoma, lung adenocarcinoma, papillary thyroid cancer) attained a PR. Optional longitudinal collection of plasma cfDNA to assess clonal evolution was performed and will be presented at the meeting.

Conclusions: Vemurafenib in combination with crizotinib or sorafenib is well tolerated with encouraging activity including patients previously treated with BRAF/MEK inhibitors.

Clinical trial identification: NCT01531361

Legal entity responsible for the study: MD Anderson Cancer Center

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Disclosure: F. Janku: Research funding: Novartis, Genentech, BioMed Valley Discoveries. Scientific Advisory Board: Novartis. All other authors have declared no conflicts of interest.

405P Hepatic functional imaging and genomics to predict irinotecan pharmacokinetics and pharmacodynamics: The PREDICT IR study

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Background: Body surface area-based dosing of Irinotecan (IR), has not accounted for its significant pharmacokinetic (PK) and pharmacodynamic (PD) variability. Given IR's unique metabolism, hepatic functional nuclear imaging (HNI) with probes for hepatic transporters correlated with its PK. This study further evaluated the utility of HNI combined with extensive excretory/metabolic/PD pharmacogenomics (PG) to predict IR PK and PD in patients (pts) treated with FOLFIRI to enable dose individualization.

Methods: Eligible pts had advanced colorectal cancer, suitable for $1^{st}/2^{nd}$-line FOLFIRI± Bevacizumab. Pts had blood analyzed by Affymetrix DMET™ Plus Array and additional SNPs were genotyped. For HNI, pts were given IV 250MBq ^{99m}Tc-IDA and imaging data analyzed for hepatic extraction/excretion parameters (clearance [CL], 1hour retention [1hRET], deconvulutional CL [DeCL], hepatic extraction fraction [HEF]). Pts treated with chemotherapy, q2-weekly, and restaged after 4 cycles. Blood taken for IR and metabolite (SN38, SN38G) analysis on day 1 cycle 1, PK parameters derived by non-compartmental analysis. Statistical correlations were evaluated between (i) IDA HNI and (2) PGs, with IR PK, toxicity, objective response (ORR) and progression-free survival (PFS).

Results: 32 pts analysed, 31 pts completed 4 cycles. (1) PK correlates: (a) HNI CL and 1hRET with SN38 Metabolic CL, ($P = 0.04$) and (b) HNI DeCL with IR $AUC_{(0\text{-}\infty)}$ ($P = 0.04$). (2) Grade 3+ diarrhea ($N = 4$, 13%) predicted by SN38 $AUC_{(0\text{-}\infty)}$ andMetabolic CL ($P = 0.04$), and gene variants for SCL22A2 and -28A3, ABCC2, UGT2B17, CYP2C18 and DPYD ($P < 0.05$) (3) Grade 3+ neutropenia ($N = 9$, 28%) predicted by SN38 PK exposure ($P < 0.02$), HNI CL and 1hRET ($P < 0.0001$) and variants for SLC7A7-, SLC22A2-, CHST1-, UGT1A1-, -2B7, ABCB1. (4) ORR ($N = 6$, 20%) predicted by Methylene tetrahydrofolate reductase (MTHFR) 677C > T ($P = 0.002$), SN38 exposure ($P < 0.003$), and variants in metabolic/transporter genes ($P < 0.05$). (5) PFS by SN38 PK exposure, MTHFR 677C > T, HNI CL, HNI HEF and variants in PK genes ($P < 0.05$).

Conclusions: Hepatic functional imaging with extensive pharmacogenomics correlated with Irinotecan PK and PD enabling the future development of nomograms to individualize its dosing.

Clinical trial identification: Australian Clinical Trials Registry: ACTRN12610000898055

Legal entity responsible for the study: Peter MacCallum Cancer Centre

Funding: Australian Federal Government: National Health and Medical Research Council Project Grant

Disclosure: All authors have declared no conflicts of interest.

406P Ongoing phase 1 trial of SL-801, a novel XPO-1 inhibitor, in patients with advanced solid tumors; Interim results

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Background: Exportin-1 (XPO1) is a critical nuclear export protein involved in nuclear-cytoplasmic transport and is overexpressed in multiple malignancies. SL-801 is a novel oral small molecule inhibitor of XPO1 and has shown potent in vitro and in vivo anti-tumor activity against a broad range of hematologic and solid malignancies. SL-801 has been shown to reversibly inhibit XPO1, which may translate to selective activity and potential safety benefits. Study SL-801-0115 is a first-in-human, dose-escalation study in adult patients with locally advanced, unresectable or metastatic solid tumors that are resistant to or relapsed following available standard systemic therapy. Preliminary interim results in the ongoing dose-escalation Phase 1 clinical study are reported.

Methods: The objective of this multicenter, dose-escalation phase 1 trial is to evaluate the safety and tolerability of SL-801, identify the maximum tolerated dose (MTD), and assess pharmacokinetics (PK) with increasing doses. SL-801 is administered daily on Day 1 through Day 4 and Day 8 through Day 11 every 21 days. The starting dose cohort was 5 mg and has reached 35 mg to date.

Results: As of 3/31/17, 19 heavily pretreated (range: 1-11 prior therapies) adult patients with advanced solid tumors have received SL-801 (6 Females, 13 Males). Median age is 62 years (range: 39-75). MTD has not been reached. Median follow-up is 1.4 months (range: 0.1-4.9). Pharmacokinetic analyses are ongoing. The most frequent treatment-related Grade 1-2 AEs were fatigue and nausea (26%), diarrhea (16%), and myalgia, vomiting and decreased appetite (11% each). Grade 3 AEs, possibly treatment-related, included diarrhea ($n = 1$; 5 mg) and acute renal injury ($n = 1$; 30 mg). There were no grade 4 or 5 treatment-related events. Three patients achieved stable disease, for 3-7 cycles, by investigator assessment.

Conclusions: The initial dose-escalation of SL-801 appears to be well tolerated to date in patients with advanced solid malignancies. Enrollment continues in this ongoing Phase 1 trial and updated safety and efficacy data will be presented. Clinical trial information: NCT02667873.

Clinical trial identification: NCT02667873

Legal entity responsible for the study: Stemline Therapeutics

Funding: Stemline Therapeutics

Disclosure: A. Olguin, J. Bullington, S. Shemesh, J. Chen: Stemline Therapeutics: employment, stock options. C. Brooks: Stemline Therapeutics: employment, stock options, patents. All other authors have declared no conflicts of interest.

407P Antitumor efficacy of triple monoclonal antibody inhibition of epidermal growth factor receptor (EGFR) with MM-151 in EGFR-dependent and in cetuximab-resistant human colorectal cancer cells

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Background: Novel and more efficient anti-EGFR drugs capable to overcome acquired resistance to first generation of anti-EGFR inhibitors needs to be investigated.

Methods: MM151 is a mixture of three different monoclonal IgG1 antibodies directed toward three different, non-overlapping, epitopes of the EGFR. We performed an *in vivo* study by using human CRC cell lines (SW48, LIM 1215 and CACO2) which are sensitive to EGFR inhibitors, in order to evaluate the activity of MM-151 as compared to standard anti-EGFR mAbs, such as cetuximab, as single agent or in a sequential strategy of combination MM-151 with irinotecan (induction therapy) followed by MM-151 with a selective MEK1/2 inhibitor (MEKi) (maintenance therapy). Furthermore, the ability of MM-151 to overcome acquired resistance to cetuximab has been also evaluated in cetuximab-refractory CRC models.

Results: MM151 shown stronger antitumor activity as compared to cetuximab. The maintenance treatment with MM-151 plus MEKi resulted the most effective therapeutic modality. In fact, this combination caused an almost complete suppression of tumor growth in SW48, LIM 1215 and CACO2 xenografts with a mean tumor volume of 13 mm^3, 13 mm^3 and 75 mm^3, respectively at 30 week. Moreover, in this treatment group, mice with no evidence of tumor were more than double as compared to single agent treated mice. Its superior activity has also been demonstrated, in cetuximab-refractory CRC models.

Conclusions: These results provide experimental evidence that more efficient and complete EGFR blockade may determine better antitumor activity and could contribute to prevent and/or overcome acquired resistance to EGFR inhibitors.

Legal entity responsible for the study: Università degli studi della Campania, "Luigi Vanvitelli"

Funding: Associazione Italiana per la Ricerca sul Cancro (AIRC)

Disclosure: All authors have declared no conflicts of interest.

408P Validation of the Royal Marsden Hospital (RMH) prognostic score on an enriched early treatment line cohort for phase I trial patients

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Background: The RMH score has been validated to predict survival in different populations of patients starting phase I clinical trials. Most of the populations where it has been validated are of heavily treated patients that lack other treatment options. The type of phase I trials is changing and we aimed to validate the score in a new cohort with more patients treated on an early line, rahter than the usual classic phase I trials heavily pretreated patient population.

Methods: We analyzed the RMH score in the patients treated in our center in a phase I trial between 2012 and 2017. We collected demographics data, overall survival after starting the trial, the RMH score (albumin, LDH, and number of metastatic sites) for all patients and the treatment line. We considered a late line anything over two treatment lines and in any case if the patient did not have any other treatment available depending on the tumor type. An early line was the first or second treatment line when the patient did have further lines available.

Results: We treated 77 patients on a phase I trial in our institution, 23 males and 54 females. Mean age was 55 years (26-77). RMH score was (0/1/2/3) in (31/23/20/3) patients. Thirty-three patients were treated on an early line. Median survival for low score (0/1) was 639 days and for high score (2/3) was 327 days $p = 0.0834$. The mean survival for patients with low RMH score was higher than those with a high RMH score in every treatment line, although due to the low number of patients in some of those categories the difference was not significant.

Conclusions: The RMH score did predict well the overall survival in our patients. The survival times in our institution are higher than those previously published, probably due to the inclusion of patients on earlier treatment lines than those used before to calculate and validate the score. Our findings support the use of the RMH score for the selection of patients entering phase I trials irrespectively of the design of the trial (early vs. late line).

Legal entity responsible for the study: Medical Oncology Department, Hospital General Universitario Gregorio Marañón

Funding: Instituto de Investigación Sanitaria Hospital Gregorio Marañón

Disclosure: All authors have declared no conflicts of interest.

409P Updated results of phase 1 study of DS-8201a in patients with HER2 expressing non-breast, non-gastric malignancies

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Background: DS-8201a is a HER2 targeting antibody-drug conjugate of high drug to antibody ratio (7 to 8) with a novel linker and topoisomerase I inhibitor. In preclinical studies, DS-8201a showed a broad antitumor spectrum, including efficacy against low HER2 expressing breast cancer (BC) and HER2 expressing non-gastric and non-breast cancers. The current phase 1 trial includes dose escalation (Part 1) and expansion (Part 2) including BC, gastric cancer (GC) and other HER2 expressing solid tumors.

Methods: Part 1 used a mCRM to identify the recommended dose in patients (pts) with BC or GC. Part 2 was designed to evaluate the safety and efficacy in 4 expansion cohorts: HER2 positive BC, HER2 positive GC, low HER2 expressing BC, and other solid tumors expressing HER2. HER2 expression was determined by IHC, FISH, NGS or other platforms. Adverse events (AEs), objective response rate (ORR), and disease control rate (DCR: CR + PR + SD) were assessed.

Results: Twenty four pts in Part 1 and 113 pts in Part 2 were enrolled. 24 of 113 pts were HER2 expressing solid tumors other than BC and GC. DS-8201a was administered up to 8.0 mg/kg in Part 1, and dose level of 6.4 mg/kg IV every 3 weeks was chosen. DLTs were not observed in the study. In the updated Part 1 results, confirmed ORR was 35%, DCR was 91% (BC: 88%, GC: 100%), and the median duration of treatment was ≥32 weeks in heavily pretreated BC and GC pts. Non-BC and non-GC cohort consists of 11 CRC, 5 NSCLC, 4 salivary gland, 2 Paget's disease, 1 cholangiocarcinoma and 1 esophageal cancer. ORR including under confirmation and DCR were 33% and 91%, respectively in evaluable 12 pts. Two out of 5 evaluable pts with CRC and 2 out of 4 evaluable pts with salivary gland achieved PRs. Of all pts in this phase 1 study, the most common AEs of any grades were nausea (≥Gr1 60%; ≥Gr3 2%), decreased appetite (≥Gr1 55%; ≥Gr3 4%), vomiting (≥Gr1 30%; ≥Gr3 0%) and platelet count decreased (≥Gr1 30%; ≥Gr3 9%). Updated phase 1 results will be presented.

Conclusions: DS-8201a was well tolerated and is remarkably active in pts with heavily pretreated HER2 expressing BC and GC with durable disease control. Promising efficacy in HER2 expressing other tumors was observed and warrants further investigation.

Clinical trial identification: NCT02564900

Legal entity responsible for the study: Daiichi Sankyo CO., LTD.

Funding: Daiichi Sankyo CO., LTD.

Disclosure: J. Tsurutani: Paid honoraria directly by Eisai, Kyowa Hakko Kirin, Chugai, AstraZeneca, Novartis, Taiho. Paid for any consulting or advisory role by Novartis, Daiichi Sankyo, MSD, Lilly, Roche. Conducted research project funded by Daiich Sankyo, Roche, Lilly, MSD. T. Doi: Paid for consulting by Lilly, Chugai, Kyowa, Behringer, Novartis, MSD, Daiichi Sankyo, Amgen. Conducted study funded by Taiho, Novartis, Merck, Astellas, MSD, Janssen, Boehringer, Takeda, Pfizer, Lilly, Sumitomo, Chugai, Bayer, Kyowa, Daiichi Sankyo. H. Iwata: Paid honoraria directly by Daiichi Sankyo, Chugai, AstraZeneca. Paid for consulting or advisory role by Daiich Sankyo and Pfizer. Conducted research project funded by Daiich Sankyo, Chugai, AstraZeneca, Pfizer, Novartis, Eisai, MSD, Lilly. S. Takahashi: Paid honoraria directly by Eisai, Astellas, Taiho, Bayer, Daiichi Sankyo, Pfizer, AstraZeneca. Paid for consulting or advisory role by Chugai Astellas. Conducted study funded by Eisai, Chugai, MSD, Lilly, AstraZeneca, Novartis, Taiho, Daiichi Sankyo. K. Tamura: Conducted study funded by Daiichisankyo, MSD, pfizer, AstraZeneca. K. Shitara: Paid for consulting or advisory role by Chugai Pharma, Takeda, Bayer, Lilly, Bristol-Myers, Squibb. Conducted study funded by Dainippon Sumitomo Pharma, Lilly, MSD, Sanofi, Daiichi Sankyo, Taiho Pharmaceutical, Bayer, Chugai. H. Taniguchi: Honoraria for speaking or writing engagements from Takeda, Chugai, Merck Serono, Taiho, Bayer, Lilly, Yakult. Financial support for clinical trials or research found by Otsuka, Boehringer Ingelheim, MSD Oncology, Takeda. B. Li: Consulting and/or Advisory Board for Genentech, ThermoFisher Scientific, Biosceptre Australia. Principle Investigator of clinical trials supported by Genentech, AstraZeneca, BioMedValley. A. Shimomura: Conducted study funded by AstraZeneca. Y. Sato, K. Akiyama, Y. Fujisaki, C. Lee, A. Yver: Employee of Daiichi Sankyo. K. Nakagawa: Paid for any consulting or advisory role by Astellas. Ono, AstraZeneca, Boehringer Ingelheim, Daiichi Sankyo. Conducted study funded by GlaxoSmithKline, Yakult, AstraZeneca, PAREXEL, Kyowa Hakko, Otsuka, Pfizer, Astellas, Daiichi Sankyo. All other authors have declared no conflicts of interest.

410P Phase I study of the investigational, oral pan-RAF kinase inhibitor TAK-580 (MLN2480) in patients with advanced solid tumors (ST) or melanoma (MEL): Final analysis

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Background: MAPK pathway mutations leading to signaling hyperactivation are common in many ST; as RAF kinases play a key role in MAPK signaling, they represent a valid target for therapy. As a pan-RAF inhibitor, TAK-580 is differentiated from

approved BRAF-specific RAF inhibitors. Here we report the expanded cohort data from a single-agent, first-in-human study of TAK-580 (NCT01425008).

Methods: Patients with advanced ST or inoperable stage III/IV MEL received TAK-580 Q2D or QW in 28-d cycles. Primary objectives were safety and maximum tolerated doses [MTD] of TAK-580; secondary objectives included preliminary antitumor activity, PK and PD effects. Safety and PK were compared between 2 MTD regimens (200 mg Q2D vs 600 mg QW). Preliminary antitumor activity of TAK-580 Q2D vs QW was evaluated in *NRAS*-mutation positive (mut) MEL. Activity and efficacy (PFS) were assessed in *BRAF*-mut MEL. Plasma PK were assessed pre- and post-dose between d1 and d28 of cycle 1 (C1). Tumor biopsies were taken at screening and post-dose on d21 or 22 of C1. Disease assessments were performed at baseline and every 2 cycles thereafter.

Results: 80 patients received TAK-580 200 mg Q2D (60 MEL + 20 PK-evaluable ST) and 19 MEL patients received 600 mg QW. DLTs observed were: periorbital edema and maculopapular rash (280 mg Q2D); rash and hyperbilirubinemia (800 mg QW). For Q2D and QW, 41% and 32% of patients, respectively, had Gr $\geq$ 3 drug-related adverse events (AE); 19% and 11% discontinued due to AEs. Total weekly exposure (AUC_{168h}) after TAK-580 600 mg QW was comparable to 3-fold AUC_{48h} after 200 mg Q2D. Of 14 *NRAS*-mut MEL Q2D patients, 1 achieved PR (1.5 mos). In comparison, none of 17 *NRAS*-mut MEL QW patients had an objective response. 50% of the 16 *BRAF*-mut MEL Q2D patients achieved a PR with a median PFS of 4.6 mos (range 1.0–40.8).

Conclusions: The safety and PK profiles of TAK-580 Q2D and QW at MTD were acceptable. QW dosing improved safety but not efficacy over Q2D dosing. PD results were consistent with the proposed mechanism of action of TAK-580 with observed RAF pathway inhibition. These data support the use of QW dosing in the assessment TAK-580 given in combination.

Clinical trial identification: NCT01425008

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: A.J. Olszanski: Consulting or advisory role: Merck, Takeda, BMS, Kyowa Hakko Kirin, G1 Therapuetics; Research funding: Takeda, Immunocore, EMD Serono, Amgen, Incyte, Kyowa Hakko Kirin, Lilly, Advaxis, Mirati Therapuetics, Ignyta, Novartis, Pfizer, BMS, Kura; Travel/accommodation/expenses: Takeda, Churchill Pharmaceuticals, Kyowa Hakko Kirin, G1 Therapuetics. R. Gonzalez: Consultant: Bristol-Myers Squibb, Novartis, Genentech. Research support: Merck, Novartis, Genentech, Bristol-Myers Squibb, Incyte, Syndax, Takeda. P. Corrie: Advisory boards; Novartis, Pierre Fabre, Bristol-Myers Squibb, MSD, Celgene. Research funding: Celgene. Speaker honoraria: MSD, Novartis. M. Middleton: Consulting or advisory role: GSK, BMS, Amgen, Merck, Roche (all compensated); Clovis, Immunocore (both uncompensated); Travel/accommodation/expenses: Roche, Merck; Corporate-sponsored research: GSK, AZ, Eisai, Clovis, BMS, Amgen, Roche, Merck, Vertex, Immunocore, Pfizer, Medimmune. P. Lorigan: Advisory board: GSK, Novartis, Roche, Bristol-Myers Squibb, Merck, Amgen. Travel/accommodation/expenses: Bristol-Myers Squibb, MSD. A. Daud: Stock ownership: OncoSec, Inc.; Advisory board or board of directors: Novartis, Merck, Pfizer, Genentech; Corporate-sponsored research: Merck, Pfizer, Genentech, BMS. S. Zhang, E. Hoberman: Employment: Millennium Pharmaceuticals. Inc. B. Bahamon, L. Rangachari, M. Kneissl: Employment: Millennium Pharmaceuticals, Inc. D. Rasco: Corporate-sponsored research: Takeda Oncology. All other authors have declared no conflicts of interest.

411P Pharmacological activity of CB-103: An oral pan-NOTCH inhibitor with a novel mode of action

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Background: NOTCH signalling is a developmental pathway known to play critical roles during embryonic development as well as for regulation of self-renewing tissues. Aberrant activation of NOTCH signalling leads to deregulation of the self-renewal process resulting in sustained proliferation, invasion and metastasis, all of which are hallmarks of cancer. When the NOTCH pathway is inappropriately activated by genetic lesions (over expression of NOTCH ligands/receptors, GOF mutations in NOTCH receptors as well as chromosomal translocations), it becomes a major driver for NOTCH-dependent cancers and resistance to standard of care treatment. Several therapeutic approaches have been utilized to block NOTCH signalling, e.g. a) the use of monoclonal blocking antibodies (mAbs) against NOTCH ligands and receptors and b) the use of small molecule gamma-secretase inhibitors (GSIs). Here we report the pharmacological characterization of CB-103, a first-in-class orally-active small molecule, protein-protein interaction inhibitor of the NOTCH transcriptional activation complex.

Methods: Primary pharmacodynamic (PD) studies were conducted to investigate CB-103 in relation to its desired therapeutic effect for treating advanced or metastatic haematological and solid tumour malignancies as NOTCH pathway inhibitor. Regarding the PD effect, in vitro studies demonstrated for CB-103 a dose-dependent decrease in NOTCH signalling activation with a unique mechanism compared to GSIs and mAbs. In a panel of > 120 cell lines of various malignancies CB-103 was active on a subset of 24 cancer cell lines, including different solid tumours (breast, lung, sarcomas), lymphomas and leukaemias.

Results: Moreover, CB-103 demonstrated anti-NOTCH activity in the Triple-Negative Breast Cancer HCC1187 cell line, being resistant to GSIs due to a NOTCH2 chromosomal translocation. In addition, CB-103 exhibited anti-tumour efficacy in multiple in vivo models and patients derived xenograft models.

Conclusions: Safety pharmacology and toxicology studies have been completed and revealed an excellent non-clinical safety profile of CB-103. A first-in-human Phase I/IIA clinical study in advanced solid tumours and haematological malignancies is under preparation.

Legal entity responsible for the study: Cellestia Biotech AG

Funding: Cellestia Biotech AG

Disclosure: D. Weber: Chief Medical Officer of Cellestia, co-founder, stock ownership. R. Lehal: Chief Scientific Officer, co-founder, stock ownership. J-P. Bourquin: Medical advisory board Cellestia. M. Bauer: Chief Executive Officer, co-founder, stock ownership. M. Murone: Chief Operating Officer, co-founder, stock ownership. F. Radtke: Chairman of the Board, co-founder, stock ownership. All other authors have declared no conflicts of interest.

412P Design and development of potent E1 ubiquitin activating enzyme inhibitor, CPL-410-005, as novel anticancer therapy

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Background: The ubiquitin-proteasome system is crucial in tumorigenesis. The division rate of cancer cells, thus protein synthesis, is increased in comparison to normal ones, what sensitizes tumors for any protein changes. Proteasome inhibitor - bortezomib was the first inhibitor registered in treatment of blood cancers. However, drugs beneficial for solid tumors are still missing. Therefore targeting of E1 enzyme as a start of UPS pathway may serve as a promising anticancer therapy.

Methods: We have designed a novel E1 small molecule inhibitor, CPL-410-005. The inhibitory potency of compound was assessed on purified E1 enzyme, using biochemical assay. Assays to measure cellular poliubiquitylation or ubiquitin-like modifications level were developed. The compound's biological activity and selectivity was evaluated in a number of cancer cells using cell viability assays, Western Blot and flow cytometry, analyzing programmed cell death, unfolded protein response or cell cycle inhibition.

Results: CPL-410-005 inhibits E1 enzyme with greater potency than MLN7243. This results in cellular polyubiquitylation inhibition, while the impact on other ubiquitin-like modifications (neddylation, sumoilation) is minor. Tumor proliferation rate inhibition was pronounced in reference to the non-malignant cells [IC_{50} values of 20 nM for HCT-116 cells vs IC_{50} values of 400 nM for HEK293 cells]. Moreover, a higher level of unfolded protein response or programmed cell death was observed in cells treated with CPL-410-005 in reference to MLN7243 (5% apoptotic cells vs 30% for MLN7243 vs CPL-410-005, respectively). In case of CPL-410-005, apoptosis rate was higher in tumor than in normal cells (80% apoptotic cells vs 20%, respectively). A high throughput study was performed, to determine the activity of CPL-410-005 on 120 human tumor cell lines, showing that >85% tested cell lines responded with IC_{50} value below 100nM. The initial in vivo studies on tumor human xenografts are ongoing.

Conclusions: We have designed and evaluated in vitro a potent E1 inhibitor - CPL-410-005, which shows promising in vitro activity. Further preclinical studies are necessary to develop this compound as a novel anticancer therapy.

Legal entity responsible for the study: Celon Pharma

Funding: Celon Pharma

Disclosure: A. Stanczak, A. Górnicka, B. Stypik, M. Mroczkiewicz, J. Pieczykolan, K. Dubiel: Full-time employee of Celon Pharma S.A., Lomianki, Poland. M. Wieczorek: Chief Executive Officer of Celon Pharma S.A., Lomianki, Poland.

413P RX-3117, a novel hypomethylating agent, shows promising therapeutic activity in combination with nab-paclitaxel and checkpoint inhibitors in preclinical models

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Background: A novel nucleoside analogue, RX-3117, is being evaluated in a Phase IIa study in patients with advanced pancreatic and bladder cancer. RX-3117 shows promising antitumor activity in xenografts including patient-derived xenografts resistant to gemcitabine. Here we demonstrate the preclinical effects of combination therapy with RX-3117 + Abraxane or anti-PD1 immunotherapy.

Methods: One colorectal (MC38), pancreatic (Pan02) syngeneic xenograft and patient-derived pancreatic (CTG-0723) xenograft model were exposed to 60 mg/kg RX-3117 po, 5 days on, 2 days off for three weeks. Pan02 and MC38 received RX-3117 alone or in combination with 100ug anti-PD1, ip. PDx CTG-0723 received one cycle of RX-3117, followed by a second cycle of RX-3117 + 10 mg/kg Abraxane, iv. MC38 tumor-infiltrating lymphocytes were measured at days 5 and 12 with RX-3117.

Results: In MC38 at day 28, RX-3117 or anti-PD1 showed TGIs of 90% and 93%, whereas the combination showed 99% TGI. Differences were also observed in TILs.

Relative to vehicle (CD4+:10.6+/-1.6, CD8+: 8.6+/-1.1), %CD4 + (17.4+/-1.4) and CD8+ cells (12.3+/-1) increased. %MDSCs decreased on Day 5 in blood (42+/-7.7 vs 29+/-6). %CD8+ increased (9.6+/-3.3 vs 12.3+/-3.2) and %MDSC decreased (15.4 +/- 3.7 vs 10.6 +/- 3.3) in tumor on Day 12. In Pan02, RX-3117 + anti-PD1 resulted in a day 32 TGI of 60%. Anti-PD1 alone had a day 32 28% TGI. In CTG-0723, the first cycle of RX-3117 at 10, 30 and 60 mg/kg produced TGIs of 33%, 46% and 77%. The second cycle, RX-3117 + Abraxane, day 46 TV showed TGIs of 55%, 58% and 83%.

Conclusions: We demonstrate the antitumor effect of RX-3117 as a single agent and in combination with Abraxane or anti-PD-1. The combination of RX-3117/anti-PD1 in MC38 produced 7 tumor-free survivors out of 10 compared to 2 of 10 by anti-PD1 alone, indicating RX-3117 may mobilize the right population of lymphocytes to enable anti-PD-1 to work more effectively. In Pan02, RX-3117 exhibited better TGI than anti-PD-1. In CTG-0723, the combination of RX-3117 and Abraxane showed additive TGI. These studies demonstrate the therapeutic potential of RX-3117 in multiple cancers and validate the combination of RX-3117 with anti-PD1 in several cancer types.

Legal entity responsible for the study: Rexahn Pharmaceuticals, Inc.

Funding: Rexahn Pharmaceuticals, Inc

Disclosure: J. Frank, Y.B. Lee, D.J. Kim: Employee of Rexahn Pharmaceuticals. E. Benaim: Officer at Rexahn Pharmaceuticals, employee, stock-holder.

414P A phase Ib trial of JX-594 (Pexa-Vec), a targeted multimechanistic oncolytic vaccinia virus, in combination with low-dose cyclophosphamide in patients with advanced solid tumors

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Background: JX-594 (Pexa-Vec) is a targeted oncolytic vaccinia virus designed to selectively replicate in and destroy cancer cells with epidermal growth factor receptor (EGFR)/ras pathway activation. Direct oncolysis plus GM-CSF expression is accompanied by tumor vascular disruption and anti-tumoral immunity. JX-594 was well-tolerated intravenously (IV) and intratumorally (IT). Given the immunomodulatory effects of low-dose cyclophosphamide (CP), anti-tumor synergy is predicted with JX-594.

Methods: CP was delivered orally at the dose of 50 mg BID one week on one week off. JX-594 was delivered IV at day 8 of each day 28-cycle. 2 dose levels of JX-594 were explored: 3.10^8 and 1.10^9 plaque forming units (pfu). The primary objective of the study was to determine the safety of JX-594 in combination with low-dose CP in patients with advanced solid tumors. Secondary objectives include response rates, PFS, pharmacokinetics and pharmacodynamics.

Results: Ten patients entered the study. 9 were evaluable for safety. No dose limiting toxicity was observed. The combination regimen was well-tolerated. The most frequent adverse events were grade 1-2 fever/transient flu-like symptoms (n = 10), grade 1-2 nausea (n = 5), grade 1-2 anemia (n = 4) and grade 1-2 fatigue (n = 4). 2 patients (breast cancer, ovarian cancer) had stable disease as best overall response.

Conclusions: IV JX-594 was well-tolerated in combination with low-dose CP. PK and PD (immunological profiling) will be presented at the meeting. Two phase 2 studies are ongoing in patients with advanced HER2 negative breast cancer and advanced soft-tissue sarcomas, respectively.

Clinical trial identification: NCT02630368

Legal entity responsible for the study: Institut Bergonié

Funding: INCA

Disclosure: All authors have declared no conflicts of interest.

415P Population pharmacokinetic analysis of OT-101 (trabedersen) in patients with advanced tumors

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Background: OT-101 (Trabedersen) is a phosphorothioate antisense oligodeoxynucleotide specifically inhibiting the expression of transforming growth factor-beta 2 (TGF-b2), whose overexpression is a pivotal factor for malignant progression in solid tumors. In the clinical Phase I/II study, plasma pharmacokinetic (PK) profile of OT-101 administered intravenously was evaluated in patients with advanced tumors. A population PK model was built to further understand the factors contributing to the variability in PK of OT-101.

Methods: A total of 61 patients with pancreatic cancer (n = 37), malignant melanoma (n = 19), or colorectal carcinoma (n = 5) were treated with OT-101 with escalating doses in 2 treatment schedules (1st schedule: 7-days-on/7-days-off; 2nd schedule: 4-days-on/10-days-off; up to 10 cycles). The plasma concentration data of OT-101 were analyzed using nonlinear mixed-effect modeling (Phoenix NLME 7.0). The influence of age, gender, body mass index (BMI), body weight (BW), cancer type, treatment schedule, creatinine clearance (CrCl) and estimated glomerular filtration rate (eGFR) as covariates on PK was evaluated.

Results: With exclusion of protocol deviations, the final analysis dataset contained 92 patient cycles and 1188 plasma samples. Twenty-six patient cycles were from 7-days-on/7-days-off schedule and 66 were from 4-days-on/10-days-off schedule. The concentration time course of OT-101 was best described by a two-compartment model with combination of additive and multiplicative error. The estimates of PK parameters were as follows: total body clearance, 41.79 mL/hr; distribution volume of the central compartment, 6.30 L; inter-compartmental clearance, 4.02 L/hr; distribution volume of the peripheral compartment, 5965.83 L. eGFR were identified as the covariates on OT-101 central compartmental clearance, with K_{eGFR} as 11.45.

Conclusions: The PK profile of OT-101 was best described by a two-compartment model. The model will be used with the sparse PK samples collected from the planned phase 3 clinical trial to calculate exposure measures for use in subsequent PK-PD analysis of efficacy.

Legal entity responsible for the study: Oncotelic

Funding: None

Disclosure: W. Wang, V. Trieu, L. Hwang: Employee of Oncotelic Inc. K. Ng, D. Nam: Employee of Autotelic Inc.

417TiP A phase 1 study of oral LOXO 292 in adult patients with advanced solid tumors, including RET-fusion non-small cell lung cancer, medullary thyroid cancer and other tumors with increased RET activity

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Background: RET is a receptor tyrosine kinase with critical roles in normal physiology. Fusions of the RET kinase with a partner protein have been identified in ~2% of non-small cell lung cancers (NSCLC) and a subset of papillary thyroid cancers and other tumors. RET mutations occur in the majority of medullary thyroid cancers (MTC). Although multikinase inhibitors with anti-RET activity are in the clinic, their activity is limited by incomplete RET inhibition in patients, toxicity from off-target effects (e.g.VEGFR2) and poor pharmacokinetics (PK). LOXO-292 is a potent and specific inhibitor of RET, including fusions, activating mutations and potential acquired resistance mutations, with minimal inhibition of off targets, including > 100-fold selectivity for VEGFR2.

Trial design: This is an open label, multi-center, dose escalation and expansion Phase 1 study in adult patients with advanced solid tumors. Major eligibility criteria for dose escalation include prior cancer treatment (prior treatment with anti-RET TKIs allowed) and normal hematopoietic and major organ function. During dose escalation, when a dose level is achieved that is safe and consistent with RET target engagement, enrollment will be limited to patients with RET-fusion NSCLC, MTC and other tumors with RET alterations or increased RET activity, as identified in tumor or blood by prior molecular assays performed locally. Once the Maximum Tolerated Dose (MTD) or recommended dose for further study is identified, patients will be enrolled to one of five dose expansion cohorts, depending on tumor type (i.e. NSCLC, MTC, other cancer), prior TKI therapy and type of RET alteration. The starting dose of LOXO-292 is 20 mg orally once per day, and dose escalation is proceeding using a 3 + 3 design. The primary endpoint is establishment of the MTD/recommended dose for further study. Key secondary endpoints include: safety and tolerability, PK parameters and preliminary assessment of anti-tumor activity. Patients undergo safety, clinical and PK assessments and radiographic evaluation for their disease at regular intervals.

Clinical trial identification: Treatment of patients has begun. The study has been submitted to the NIH (https://clinicaltrials.gov) and the ClinicalTrials.gov Identifier is pending and will be provided as soon as available.

Legal entity responsible for the study: Loxo Oncology

Funding: Loxo Oncology

Disclosure: S. Smith, T. Eary, S. Cruickshank, M. Nguyen, S. Rothenberg: Ownership interest in Loxo Oncology. All other authors have declared no conflicts of interest.

418TiP Phase 1/2 study of the selective TRK inhibitor larotrectinib, in pediatric patients with cancer

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Background: Neurotrophin ligands and their receptors TRKA, TRKB, and TRKC (encoded by *NTRK1, NTRK2, and NTRK3)* are important for growth regulation, differentiation and survival of neurons. Translocations involving the *NTRK1/2/3* kinase domain have been described in a broad range of adult and pediatric tumors, including infantile fibrosarcoma (IFS), spindle-cell sarcoma, congenital mesoblastic nephroma, pediatric papillary thyroid cancer, high- and low-grade gliomas and Ph-like acute lymphoblastic leukemia. Larotrectinib is the first small-molecule selective inhibitor of TRKA, -B, and -C in clinical development and has demonstrated tumor growth inhibition in preclinical models and clinically meaningful and durable responses in patients with *NTRK*-translocated cancers in an adult phase 1 trial.

Trial design: We have initiated an open-label, multi-center, international Phase 1/2 study with larotrectinib in pediatric patients with solid tumors and primary CNS tumors. A pediatric recommended phase 2 dose of 100mg/m^2 (caped at 100mg BID) has been established. Enrollment to phase 2 began in April 2017 and is ongoing. For the phase 2 component, patients from 1-month of age with IFS or an *NTRK*-fusion positive tumor, including those who have not undergone definitive surgery are eligible. Patients who have not undergone definitive surgery are eligible as well. Larotrectinib is administered as an oral liquid formulation or capsules twice daily on a continuous 28-day schedule. Dosing is based on body surface area. The phase 2 portion enrolls patients with *NTRK*-translocated tumors and measurable disease into three cohorts: 1) infantile fibrosarcoma; 2) other extracranial solid tumors; and 3) primary CNS tumors. The primary endpoint is objective response rate, with duration of response and progression free survival as secondary efficacy endpoints. Quality of life measures and ctDNA are exploratory endpoints. Each phase 2 cohort will enroll in a single stage of up to 10 patients. Molecular abnormalities will be characterized through the analysis of archival tissue.

Clinical trial identification: NIH: NCT02637687; EudraCT #: 2016-003498-16

Legal entity responsible for the study: Loxo Oncology, Inc.

Funding: Loxo Oncology, Inc

Disclosure: M.C. Cox: Employee and stockholder of Loxo Oncology, Inc. All other authors have declared no conflicts of interest.

419TiP Chemosensitization of carboplatin by NOX66: Pharmacokinetics and safety

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Background: The experimental anti-cancer drug, idronoxil, is a selective inhibitor of PI3K/AKT in tumor cells, with studies showing it to be a potent chemosensitizing agent of carboplatin *in vitro* and in animal studies across a wide range of cancer cell types. These results, however, have not translated to clinical efficacy, with a Phase 3 study of combined oral idronoxil and intravenous carboplatin in patients with late-stage platinum-refractory ovarian cancer discontinued with no efficacy seen. This lack of efficacy is now thought to be due to complete conversion of idronoxil to bio-inactive Phase 2 metabolites. NOX66 is a suppository formulation of idronoxil designed to protect the drug from Phase 2 metabolism. This first-in-human study will look at the ability of NOX66 to deliver relatively high levels of idronoxil in a bio-active form, investigating (a) PK and (b) safety of NOX66 administration both as a monotherapy and in combination with carboplatin.

Trial design: This is an open label, Phase 1 PK and safety study of NOX66 as a monotherapy and in combination with carboplatin. Patients included have end stage, refactory solid tumours, and no further therapy options available. A total of 16 patients will be recruited into the study in two cohorts of 8 patients. NOX66 suppositories are formulated using 400mg of idronoxil per 2.2g suppository. Patients are allocated to receive either one or two suppositories per day. Study Part 1: NOX66 PK: Patients receive NOX66 for 14 consecutive days as monotherapy, with a follow up period of 7 days post-dosing. Blood samples will be collected throughout the monotherapy arm to measure levels of idronoxil. If no significant adverse events are noted in this 21 day period, a patient will continue in the study. Study Part 2: NOX66 plus Carboplatin: Patients receive NOX66 at the same dose as in Part 1, for 7 days. Carboplatin is administered on Day 2 of treatment. Up to 6 cycles of chemotherapy are administered, at intervals of 28 days. For Cycles 1-3, low dose (AUC4) carboplatin is administered. Subject to safety review, standard dose (AUC6) carboplatin is administered for cycles 4-6. Safety assessment is continued throughout the study, with measures to identify efficacy signals (CT scan, ECOG) performed at baseline and after Cycles 3 and 6.

Clinical trial identification: Trial Protocol Number: NOX66-001A Clinicaltrials.gov NCT02941523

Legal entity responsible for the study: Noxopharm Limited

Funding: Noxopharm Limited

Disclosure: I. Minns: Employee of Noxopharm Limited. G. Kelly: Member of the board of Directors, employee and a shareholder of Noxopharm Limited.

420TiP Phase 1b/2 study to assess the safety, tolerability, and clinical activity of BGB-290 in combination with temozolomide in patients with locally advanced or metastatic solid tumors

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Background: Poly (ADP-ribose) polymerase (PARP) proteins are a family of DNA binding and repair proteins and are thought to play a key role in the base excision repair of DNA damage generated by temozolomide (TMZ), a DNA-alkylating agent. PARP inhibitors (PARPis) represent a class of antitumor agents that exert their cytotoxic effects by inhibiting PARP activity. Some PARPis are capable of trapping PARP proteins on DNA, further augmenting cell death. BGB-290 is a potent and selective inhibitor of PARP1/2 and has demonstrated PARP trapping capacity. Synergistic cytotoxicity has been observed *in vitro* and *in vivo* when BGB-290 is combined with low dose TMZ.

Trial design: This open-label, Phase 1b/2 dose-escalation/dose-expansion study is designed to evaluate BGB-290 at the recommended Phase 2 dose (60 mg administered orally twice daily [PO BID]) in combination with TMZ in patients with locally advanced and metastatic solid tumors. The phase 1b dose-escalation component will follow a 3 + 3 design to establish the maximum tolerated dose (MTD) of TMZ in combination with BGB-290 in ~50 patients with solid tumors. Dose escalation will evaluate the safety, tolerability and pharmacokinetics of BGB-290 (60 mg BID) plus escalating doses

Table: 420TiP

Treatment arm	Tumor type	Estimated sample size
Cohort 1	Platinum-sensitive high grade epithelial, non-mucinous, ovarian cancer, fallopian cancer or primary peritoneal cancer with either known deleterious or suspected deleterious germline or somatic BRCA1/2 mutation or with DNA HRD	20
Cohort 2	Triple negative breast cancer with either known deleterious or suspected deleterious germline or somatic *BRCA1/2* mutation or with DNA HRD	20
Cohort 3	Metastatic castration-resistant prostate cancer with either known deleterious or suspected deleterious germline or somatic BRCA1/2 mutation or with documented HRD	20
Cohort 4	Extended stage small cell lung cancer who have been treated with ≤2 prior regimens	20
Cohort 5	Gastric or gastroesophageal junction cancer who have been treated with ≤ 2 prior regimens	20

of TMZ administered once daily (QD) either on Days 1-7 (Arm A) or continuously (Arm B) of each 28-day cycle. The phase 2 component will further evaluate the safety, tolerability and antitumor activity of the recommended combination dose and schedule in ~20 patients with one of five different tumor types (**Table**). Enrollment into these expansion cohorts will occur simultaneously and independent of each other. Subjects will continue to receive treatment in 28-day cycles until confirmed disease progression, intolerable toxicity, or discontinuation/withdrawal.

Legal entity responsible for the study: Beigene Ltd.

Funding: Beigene Ltd

Disclosure: M. Johnson: Research funding compensation for consulting to the institution from OncoMed, BerGenBio, Lilly, and various Pharm/Biotech companies. Spouse is a contract lobbyist for Astellas and Otsuka Pharmaceuticals. B. Benson, R. Wei: Employee and stock holder of BeiGene USA. R. Brachmann: Employee of BeiGene USA. M.D. Galsky: Consulting fees from Genentech, Merck, Novartis, Astellas, Astra Zeneca, and Bristol-Myers Squibb outside the submitted work; stock options in Dual Therapeutics outside the submitted work.

421TiP Phase 1b/2 study to assess the clinical effects of BGB-290 in combination with radiation therapy (RT) and/or temozolomide (TMZ) in patients with first-line or recurrent/refractory glioblastoma

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Background: Poly (ADP-ribose) polymerase (PARP) proteins are a family of DNA binding and repair proteins and are thought to play a key role in the base excision repair of DNA damage generated by TMZ. In glioblastoma (GB) cells, pharmacological modulation of PARP activity increased growth inhibition induced by TMZ in both p53-wild type and-mutant GB cells lowering the TMZ IC_{50}. RT used in the clinical treatment of GB generates mostly single-strand breaks (SSBs). In non-replicating cells PARP inhibition only delays the repair of SSBs induced by radiation with a minimal impact on cell survival. On the contrary, PARP inhibition markedly enhances radiosensitivity of proliferating cells generating double-strand breaks. Thus, PARP inhibitors have the potential to increase the therapeutic index of RT by increasing DNA damage mainly in highly replicating tumor cells, but sparing non-cycling normal tissues. BGB-290, a potent and selective inhibitor of PARP1/2, has demonstrated potent PARP trapping, brain penetrance and antitumor activity in preclinical intracranial xenograft models.

Trial design: This open-label, dose-escalation/dose-expansion Phase 1b/2 study was designed to determine the safety, tolerability, pharmacokinetics, pharmacodynamics, and antitumor effects of BGB-290 at the recommended Phase 2 dose (60 mg PO BID) in combination with RT and/or TMZ. The Phase 1b component will consist of 3 dose-escalation arms. Arm A: BGB-290 will be combined with RT in patients with first-line GB with unmethylated *MGMT* promoter ('unmethylated GB'); Arm B: BGB-290 will be combined with both TMZ and RT in patients with first-line unmethylated GB; Arm C: BGB-290 will be combined with increasing doses of TMZ in patients with recurrent/refractory methylated or unmethylated GB. Once a recommended Phase 2 regimen has been established, up to 60 patients may be enrolled in the dose-expansion (Phase 2) cohort for that arm. In Arm C, 2 expansion cohorts with up to 60 patients each may be opened: 1 for unmethylated GB and 1 for methylated GB.

Legal entity responsible for the study: Beigene Ltd.

Funding: Beigene Ltd.

Disclosure: P. Wen: Grants, personal fees, and/or non-financial support from Agios, Angiochem, AstraZeneca, Genentech/Roche, GlaxoSmithKline, Immunocellular Therapeutics, Karyopharm, Merck, Novartis, and other biotech/pharma companies outside submitted work. D. Schiff: Grants from Cavion & Celldex, personal fees from VBI, Orbus, Monteris, Genentech-Roche, Heron Pharmaceuticals, Midatech, and Oxigene, outside the submitted work. R. Brachmann: Employee of Beigene USA, Inc. R. Weitzman: Consultant to BeiGene. T. Cloughesy: Personal fees from Pfizer, Tocagen, Roche, Novocure, Nektar, VBL, ABBVIE, Upshire Smith, Notable Labs, Oxigene, NewGen, Agios, Cortice, MedQia, PRoNai,and other pharma/biotech companies, outside the submitted work. All other authors have declared no conflicts of interest.

422TiP PROCLAIM-CX-2009: A first-in-human trial to evaluate CX-2009 in adults with metastatic or locally advanced unresectable solid tumors

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Background: CX-2009 is a novel recombinant Probody™ drug conjugate (PDC) derived from a humanized monoclonal antibody (mAb) against CD166 and conjugated to N-succinimidyl 4-(2-pyridyldithio) butanoate-N2′-deacetyl-N2′-(4-mercapto-4-methyl-1-oxopentyl)-maytansine (SPDB-DM4, licensed from Immunogen), a potent microtubule inhibitor. PDCs are fully recombinant mAb prodrugs designed to remain inactive until they are cleaved into an active mAb by tumor-associated proteases. This tumor-specific activation allows PDCs to target highly and homogeneously expressed tumor antigens while avoiding binding to these same targets on healthy tissue. An example is CD166 (also referred to as activated leukocyte cell adhesion molecule [ALCAM]), which is highly expressed in multiple cancers but also in healthy tissue. In preclinical studies, CX-2009 exhibited antitumor activity and reduced peripheral binding compared to the corresponding anti-CD166 ADC.

Trial design: PROCLAIM-CX-2009 (PRObody CLinical Assessment In Man) is an open-label, multicenter, dose-escalation study to determine the maximum tolerated dose (MTD) and the recommended phase 2 dose (RP2D) of CX-2009 in 7 selected tumor types with high CD166 expression (breast, lung, prostate, ovarian, endometrial, head and neck, and biliary carcinomas). Part A ($n \leq 50$) will initiate with accelerated dose titration, followed by a standard 3 + 3 design to determine the MTD and ending in a modified toxicity probability interval 2-design cohort treated at the MTD to determine the RP2D. Part B of the study will be a dose expansion phase testing CX-2009 administered at the RP2D in the same 7 tumor types (up to 14 patients each, $n \leq 98$). Eligibility is based on confirmed refractory metastatic or locally advanced unresectable tumor. Outcome measures include assessment of safety, tolerability, pharmacokinetics, and efficacy based on RECIST 1.1. Exploratory biomarkers will characterize tumor CD166 expression and mitotic markers as well as CX-2009 activation in tumor versus peripheral blood.

Clinical trial identification: NCT03149549

Legal entity responsible for the study: CytomX Therapeutics, South San Francisco, CA, USA

Funding: CytomX Therapeutics, South San Francisco, CA, USA

Disclosure: M. Middleton: Grants: Roche, AstraZeneca, GSK. Advisory board: Amgen, Novartis, Rigontec, CytomX. Personal fees: Amgen, Roche, GSK, Novartis, Bristol-Myers Squibb, Eisai, Merck, CytomX. A. Yang Weaver, M. Will: Employee of CytomX Therapeutics. J. Harding: Consultant to Bristol-Myers Squibb. All other authors have declared no conflicts of interest.

423TiP The first-in-human, dose-finding PROCLAIM-CX-072 trial to assess the antitumor activity and tolerability of the probody therapeutic CX-072 as monotherapy and in combination with ipilimumab or vemurafenib in solid advanced tumors and lymphomas

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Background: CX-072 is a novel protease activatable prodrug (Probody™ therapeutic) derived from a human monoclonal antibody against programmed cell death ligand 1 (PD-L1). CX-072 was designed to restrict its activity to the tumor microenvironment and remain largely inactive in nonmalignant tissue. A surrogate molecule for CX-072 displayed potent antitumor activity with reduced systemic immune activation and immune-related toxicities in preclinical tumor models, potentially enabling new and more effective combination therapies. The phase 1/2 PROCLAIM-CX-072 (PRObody CLinical Assessment In Man) study will assess the safety, tolerability, and antitumor activity of CX-072, as monotherapy and in combination, in adults with advanced or recurrent solid tumors and lymphomas.

Trial design: In an open-label, multicenter, dose-escalation, 3 + 3 design, CX-072 will be administered as monotherapy (Part A) in 2 combination schedules with ipilimumab 3 mg/kg 3 weekly × 4 (Parts B1 and B2) and in combination with vemurafenib 960 mg/kg twice daily (Part C). The expansion cohort (Part D) will include CX-072

monotherapy in PD-L1–responsive tumor types. Patient recruitment was initiated on January 11, 2017. Key inclusion criteria are: Parts A and B1—advanced, refractory solid tumor or lymphoma in checkpoint inhibitor-naive patients for whom approved PD agents are not available; Part B2—advanced, refractory solid tumors or lymphomas with measurable disease that progressed on previous treatment with a PD-1/PD-L1 inhibitor but patients did not discontinue due to toxicity; Part C—checkpoint inhibitor, BRAF-inhibitor, and MEK-inhibitor-naive metastatic V600E BRAF-mutated melanoma. Efficacy will be determined according to irRECIST v1.1 criteria, and safety and tolerability will be assessed based on the incidence and nature of dose-limiting toxicities, adverse events (AEs), and serious AEs. Exploratory biomarkers will be used to characterize tumor protease activity, immune response pattern within the tumor, and CX-072 activation in tumor vs peripheral blood.

Clinical trial identification: NCT03013491

Legal entity responsible for the study: CytomX Therapeutics, South San Francisco, CA, USA

Funding: CytomX Therapeutics, South San Francisco, CA, USA

Disclosure: J. Wydmanski: Consultant to Bristol-Myers Squibb. B. Irving, M. Will: Employee of CytomX Therapeutics. F. Thistlethwaite: Personal fees from Novartis, Bristol-Myers Squibb, Pfizer, and Ipsen. All other authors have declared no conflicts of interest.

424TiP Phase 1b multi-indication study of the antibody drug conjugate anetumab ravtansine in patients with mesothelin-expressing advanced or recurrent malignancies

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Background: Mesothelin is expressed in a wide variety of tumours, including mesothelioma, ovarian, pancreatic, gastric/GEJ, NSCLC, triple-negative breast cancer, cholangiocarcinoma, and thymic carcinomas. Anetumab ravtansine (BAY 94-9343), is a novel fully human anti-mesothelin IgG1 antibody conjugated to the maytansinoid tubulin inhibitor DM4 and has shown encouraging anti-tumor activity in mesothelioma and ovarian cancer patients in a phase I study. We will therefore conduct a signal generating study with anetumab ravtansine in six additional high unmet medical need malignancies with mesothelin expression (NCT03102320).

Trial design: Eligibility criteria include: ≥18 years, unresectable locally advanced or metastatic recurrent or relapsing disease, one or more prior lines of therapy, and availability of tumour tissue for mesothelin expression testing. Mesothelin-positive patients with selected adenocarcinomas (NSCLC, triple negative breast, gastric including gastroesophageal junction) and thymic carcinoma will receive anetumab ravtansine as monotherapy at 6.5 mg/kg IV on a 21-day cycle. Patients with cholangiocarcinoma will receive anetumab ravtansine in combination with cisplatin (25 mg/m2 IV day 1 and 8 on a 21-day cycle for up to 6 cycles) and patients with pancreatic adenocarcinoma will receive anetumab ravtansine in combination with gemcitabine (1000 mg/m2 IV day 1 and 8 on a 21-day cycle). A safety run-in phase (18-24 patients each) will be conducted for the combination regimens prior to enrolling patients in the main study phase. The primary objective of the main phase of the study is objective response rate (ORR) of anetumab ravtansine as monotherapy or combination therapy in patients with either of two mesothelin expression levels: high (≥30% positive tumor cells with moderate and stronger membrane staining intensity) and low-mid (≥5% all intensities and <30% positive tumour cells with moderate and stronger membrane staining intensity). Secondary objectives include safety, disease control rate, duration of response, durable response rate, and progression-free survival. Approximately 348 patients will be enrolled.

Clinical trial identification: NCT03102320

Legal entity responsible for the study: Bayer AG

Funding: Bayer AG

Disclosure: A. Walter: Employee of Bayer AG. L. Cupit, J. Siegel, A. Holynskyj, B.H. Childs, C. Elbi: Employee of Bayer HealthCare Pharmaceuticals Inc. All other authors have declared no conflicts of interest.

425TiP A phase 1 study of SY-1365, a selective CDK7 inhibitor, in adult patients with advanced solid tumors

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Background: SY-1365 is a selective and potent covalent CDK7 inhibitor. CDK7 activity has been implicated in malignancies with transcriptional dependencies such as SCLC, TNBC, ovarian cancer, MYCN-amplified neuroblastoma, and various hematologic malignancies including AML and T-ALL. Preclinical studies in solid tumor and hematologic malignancies show treatment with SY-1365 leads to antitumor activity, showing apoptosis in vitro and complete regressions in xenograft models. This first clinical study is focused on patients with advanced solid tumors. The primary objectives are to assess the safety and tolerability of SY-1365 administered intravenously as a single agent, and to determine dose-limiting toxicities, maximum tolerated dose, and the recommended phase 2 dose. Secondary objectives include evaluation of pharmacokinetic (PK) properties and pharmacodynamic (PD) effects of SY-1365 in tumor and surrogate tissues, as well as assessment of preliminary anti-tumor activity.

Trial design: This is a multi-center, open-label Phase 1 trial that is expected to enroll approximately 70 patients with advanced solid tumors. The dose escalation phase of the trial is open to solid tumor patients for whom standard curative or palliative measures do not exist or are no longer effective. Initially, SY-1365 will be administered intravenously twice weekly for 3 weeks of each 4-week cycle. Regimen optimization will be based upon PK, PD, and safety data prior to an expansion phase to evaluate preliminary antitumor activity of SY-1365 in 25 patients with SCLC, TNBC or ovarian cancer. A second expansion cohort will enroll 10 patients with tumors of any histology to evaluate PD endpoints in paired tumor biopsies. SY-1365 target engagement in peripheral blood mononuclear cells and available tumor biopsies will be assessed by measuring CDK7 occupancy over the course of treatment. Downstream biological pathway impact of SY-1365 will be measured by quantifying changes in gene expression as a result of transcriptional inhibition. Induction of tumor cell apoptosis will also be investigated. This trial opened in May 2017. ClinicalTrials.gov identifier: NCT03134638.

Clinical trial identification: Study Protocol Number: SY-1365-101. ClinicalTrials.gov NCT03134638

Legal entity responsible for the study: Syros Pharmaceuticals, Inc

Funding: Syros Pharmaceuticals, Inc

Disclosure: A. Tolcher: Co-owner of South Texas Acelerated Research Therapeutics which receives fees for consulting and board memberships from companies (17); and research funding from companies (34) for his role as principle investigator. E. di Tomaso: Employee and stock owner of Syros Pharamceuticals. N. Waters, D.A. Roth, K. Stephens: An employee and stock holder of Syros Pharmaceuticals. G. Shapiro: Advisory boards for Pfizer, Lilly, G1 Therapeutics, Roche and Vertex Pharmaceuticals. Research funding from Pfizer and Lilly for CDK inhibitor-based projects. All other authors have declared no conflicts of interest.

426TiP First-in-human study of AMC303 as monotherapy in patients with advanced solid tumor of epithelial origin

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Background: CD44v6 is an isoform of the CD44 family of transmembrane glycoproteins for hyaluronan. High CD44v6 expression was correlated with tumor invasion, metastasis, recurrence and chemoresistance. CD44v6 is a co-receptor of the receptor tyrosine kinases c-Met, RON and VEGFR-2 that play a critical role in the development and progression of many types of cancer. Inhibition of CD44v6 efficiently blocks activation of c-Met, RON and VEGFR-2 and intracellular downstream signaling processes. AMC303 is a highly specific and selective inhibitor of CD44v6 for which strong anti-tumor activity was demonstrated *in vitro* and *in vivo*. In xenotransplantation animal models, intermittent application of AMC303 resulted in a marked reduction of the primary tumor, prevention of metastatic spread and regression of existing metastases. Good safety and tolerability were demonstrated in pre-clinical studies. The starting dose of 0.1 mg/kg and dose escalation steps are based on the safety profile and are supported by modelling of human pharmacokinetic (PK) profiles from animal exposure studies. Blocking of CD44v6 by AMC303 represents a novel and promising approach to block cancer related RTK pathways by an extracellular acting drug.

Trial design: A First-in-Human Phase I/Ib study in cancer patients was initiated (NCT03009214). The study was designed as a two part open-label, non-randomized, multicentre, dose escalation study with a 3 + 3 design (Part 1) and an expansion cohort at the Maximum Tolerated Dose (MTD)/Recommended Phase 2 Dose (RP2D) (Part 2). Inclusion and exclusion criteria are: Type of cancer (e.g. epithelial cancer for which CD44v6 is known to be highly expressed), ECOG status 0-2, and adequate hematological, renal and hepatic function. Cancer patients are enrolled after failure of conventional therapy or for whom no standard treatment is available. The primary endpoints in Part 1 are safety and tolerability and PK properties. The effects of AMC303 on RTK pathways are analysed in plasma samples (ELISA and Luminex) and mandatory tumor biopsies (immunohistochemistry, protein profiling). Part 2 will focus on selected tumor types as evaluated from the pharmacological effects of AMC303 in part 1.

Clinical trial identification: EudraCT number: 2016-001358-16

Legal entity responsible for the study: Amcure GmbH

Funding: None

Disclosure: H. Bender, K. Dembowsky: Employee by amcure GmbH and stock holder. All other authors have declared no conflicts of interest.

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

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ENDOCRINE AND NEUROENDOCRINE TUMOURS

427O Pembrolizumab for patients with PD-L1–positive advanced carcinoid or pancreatic neuroendocrine tumors: Results from the KEYNOTE-028 study

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Background: Among patients (pts) with advanced carcinoid/neuroendocrine tumors (NETs), expression of PD-L1 is associated with higher tumor grade. The multicohort phase 1b KEYNOTE-028 study (NCT02054806) evaluated safety and efficacy of pembrolizumab in pts with PD-L1–positive advanced solid tumors. This is the first report from the carcinoid and pancreatic NET (pNET) cohorts of this study.

Methods: Eligibility criteria included: Carcinoid tumors or well- or moderately differentiated pNETs; PD-L1–positive (≥1% modified proportion score or interface pattern, QualTek IHC); failure of standard therapy; and ECOG PS ≤ 1. Pts received pembrolizumab 10 mg/kg Q2W for up to 2 y or until confirmed progression, intolerable toxicity, or consent withdrawal. Response was assessed every 8 wk for 6 mo then every 12 wk. The primary endpoint was ORR per RECIST v1.1 by investigator review.

Results: 276 screened pts had tumor samples evaluable for PD-L1; 36% were positive. Among enrolled carcinoid (n = 25 [lung, n = 9; gut, n = 7; other, n = 9]) and pNET (n = 16) pts, respectively, median ages were 63 y and 61 y, 76% and 38% had ECOG PS of 1, and 44% and 50% had ≥2 prior therapies for metastatic disease. As of Jan 10, 2017, median (range) follow up was 18.9 (2.0–33.3) and 20.1 (4.5–30.4) mo. Treatment-related AEs (TRAEs) occurred in 17 (68%) carcinoid and 11 (69%) pNET pts; the most frequent (≥20%) were diarrhea (n = 7, 28%) and fatigue (n = 5, 20%) in carcinoid pts and fatigue (n = 6, 38%) and diarrhea (n = 4, 25%) in pNET pts. Grade ≥3 TRAEs occurred in 8 (32%) carcinoid pts (including diarrhea, n = 3; AST increased, n = 2; ALT increased; n = 2) and 0 pNET pts. One grade 4 AE (increased gamma-glutamyl transferase) and 1 death (unspecified cause) occurred in the carcinoid cohort; neither was treatment related. Three carcinoid pts (12%; 95% CI, 3%–31%) and 1 pNET pt (6%; 95% CI, 0%–30%) had objective responses; SD rates were 60% (n = 15) and 88% (n = 14). Durations of response were 6.9, 9.2, and 11.1 mo for the carcinoid responders; the pNET responder has an ongoing response of 17.6 mo.

Conclusions: In pts with heavily pretreated carcinoid/pNET tumors, pembrolizumab was generally well tolerated and, in some pts, provided clinically meaningful antitumor activity.

Clinical trial identification: ClinicalTrials.gov, NCT02054806; EudraCT Number, 2013-004507-39

Legal entity responsible for the study: Merck & Co., Inc., Kenilworth, NJ, USA

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428O Immune landscape of pancreatic neuroendocrine tumours (PanNETs)

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Background: To date little is known about the immune landscape of PanNETs and if immunotherapy could play a role in their treatment. We previously identified 3 molecular subtypes in PanNETs: Metastases like primary (MLP), intermediate and insulinoma like tumours (PanNETassigner signature, Sadanandam Cancer Discovery 2015). Here we sought to profile the immune architecture of 48 PanNET patient samples across these subtypes.

Methods: Patients were recruited by the ARC-Net Research Centre Verona, within an ethically approved protocol. Quality RNA was isolated from fresh frozen samples for immune profiling using microarrays, nCounter platform (Nanostring Technology) and RNAseq (Illumina). CIBERSORT analysis was performed to assess immune cell enrichment.

Results: 48 PanNET samples were classified using the PanNETassigner gene signature. Based on immune expression profile analysis, tumours were divided into two categories, immune high or immune dormant. The majority of the MLP subtype were immune high, whereas most of the insulinoma and intermediate samples were immune dormant. A small number of insulinoma samples were immune high reflecting the heterogeneity of this tumour. Within the MLP subtype there was increased expression of *CD8B*, *LAG3*, *CD38*, *CXCL10*, *CXCL9*, *CCL19*, *CD28* and *CD27* compared to the other subtypes. Some of these genes are associated with chronic infection (CD38, CXCL10) whilst others are markers of T cell exhaustion (*LAG3*). This pattern is consistent with CIBERSORT analysis conducted using microarray data on an overlapping cohort of PanNET samples, where the MLP subtype was associated with increased levels of infiltrating T cells but also an increase in exhausted CD8+ve T cells. PD1 was highly expressed in 2/15 MLPs. PDL1 expression was heterogeneous in MLP but high in 7/13 insulinomas. FOXP3 was highly expressed in a subset of the MLP samples (7/16).

Conclusions: We have demonstrated the differential expression of immune related genes across 3 known PanNET subtypes. The MLP subtype appears to be associated with an immune profile similar to that seen in chronic infection with increased T-cell exhaustion. Such detailed profiling is essential to inform patient selection approaches for immunotherapy and rational immunotherapy combinations for panNETs in the future.

Legal entity responsible for the study: Institute of Cancer Research

Funding: NIHR Biomedical Research Centre at The Royal Marsden NHS Foundation Trust and The Institute of Cancer Research, London

Disclosure: All authors have declared no conflicts of interest.

429O A phase II trial of palbociclib in metastatic grade 1/2 pancreatic neuroendocrine tumors: The PALBONET study on behalf of the Spanish Taskforce Group of Neuroendocrine Tumors (GETNE)

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Background: Overexpression or amplification of cell cycle regulators like cyclin-dependent kinase-4 (Cdk-4), phospho-Rb1, or cyclin D1 are observed in 58%, 68%, and 68% pancreatic neuroendocrine tumors (pNETs), respectively. Moreover, these alterations correlate with a more aggressive behavior. Palbociclib targets Cdk-4/6 and has shown in vitro activity in pNETs cell lines overexpressing Cdk-4.

Methods: In this non-randomized, open-label, phase II study, patients (pts) with metastatic grade (G) 1/2 pNETs were recruited from 10 centres belonging to the Spanish Taskforce Group of NETS (GETNE). Palbociclib 125 mg was given once daily for 21 of 28 days until disease progression (DP) or unacceptable toxicity. The initial planned recruitment was 21 patients based on a 2-stage Simon's phase II design, where palbociclib would be considered inactive if < 5% of patients achieved an objective response rate (ORR) by RECIST criteria. Type I error rate was 5% and the design had 85% power to reject null hypothesis when the true ORR was 5%.

Results: 21 pts were included. One pt withdrew from the study due to clinical deterioration after < 1 month (m). 54% were males, mean age was 54 years (range: 33-66), and 67% had received > 3 previous lines of therapy (23.8% pazopanib; 80.9% sunitinib; 47.6% everolimus) beside somatostatin analogs. 20 pts were evaluable for ORR with a median follow up of 10m (4.23-12.43). No responses (0%) were observed; 11 (55%) pts had stable disease and 6 of them lasted more than 6m; 7 (35%) pts had progression as best response. 1 pt had tumor shrinkage of 8%. Median PFS was 1.9m (IC95% 0 - 13). Median OS was 16.6m (IC95% 9.3 – 23.9). Most frequent toxicities of any grade were: asthenia (16.2%), diarrhea (6.4%), abdominal pain (4.7%), nausea (4.3%) and neutropenia (11.5%). 5 pts developed G3-4 neutropenia (1 case of febrile neutropenia) and 2 pts G3-4 thrombocitopenia.

Conclusions: Lack of activity was observed with palbociclib in 21 molecularly unselected and heavily pretreated patients with advanced G1/2 pNETs. Translational studies correlating activity with molecular tumor markers and Ki67 proliferation index are ongoing.

Clinical trial identification: EudraCT: 2014-003924-34

Legal entity responsible for the study: GETNE (Spanish Taskforce Group for Neuroendorine Tumors)

Funding: Pfizer

Disclosure: E. Grande Pulido: Advisor for Ipsen, Pfizer, Lexicon. Scientific lectures for Pfizer and Ipsen. All other authors have declared no conflicts of interest.

430O Different RNA expression profile defines prognosis in grade 1/2 neuroendocrine neoplasms of small intestine origin: The GETNE-NETSEQ study

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Background: Neuroendocrine neoplasms (NENs) are a heterogeneous group of tumors with different prognosis. Clinical and pathological factors are used to predict outcome but there are some patients that have a poor outcome even with good classical prognostic factors. We aimed to define a different RNA expression profile (EP) that could detect patients with worse prognosis and identify possible targetable new pathways.

Methods: We identified 48 paraffin-embedded archival tumor material of patients with metastatic grade 1/2 NENs of small intestine origin for RNAseq. We generated on average 66 million paired-end reads for each sample on HiSeq2500 (Illumina). RNAseq reads were mapped against the human reference genome (hg19) with Tophat (v2.0.14) and quantified using Cufflinks tools suite (v.2.2.1). 41 samples had sufficient quality to be included in the analysis. We used multivariate Cox proportional models to study the association between EP, clinical variables (gender, age, location of metastases, hormone production and Ki67 index) and overall survival (OS). We defined as poor outcome those patients that died within the first 3 years of the diagnosis of advanced disease.

Results: 9348 transcripts were quantified. A gene signature of 329 transcripts was defined by a two-way statistical analysis between poor and long term survivors. A pathway enrichment analysis of these genes showed a deregulation in the poor prognosis group on the PI3KCA-Akt-mTOR and the Toll-like receptor signaling pathways. The hazard ratio (HR) for mOS defined by EP comparing poor and long term survivor groups was 0.33, 95% CI 0.1-1.1, p = 0.081 in the univariate analysis and HR of 0.05, 95% CI 0.005-0.51, p = 0.011 in the multivariate analysis.

Conclusions: We identified statistically different RNA-clusters and different deregulated pathways for those patients with advanced NENs of small intestine origin with poor prognosis. To our knowledge, this is the first time that Toll-like pathway is involved in the pathogenesis of NENs. These results are relevant as they may help improve the prognosis stratification of patients and involve novel targetable pathways of great clinical potential.

Legal entity responsible for the study: Vall d'Hebron Institute of Oncology

Funding: Spanish Task Force for Neuroendocrine and Endocrine Tumors (GETNE)

Disclosure: All authors have declared no conflicts of interest.

431O Genomic subtypes of pulmonary large cell neuroendocrine carcinoma (LCNEC) may predict chemotherapy outcome

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Background: Whether to treat LCNEC with non-small cell lung carcinoma type chemotherapy (NSCLC, i.e. platinum-gemcitabine/taxanes or pemetrexed) or small cell lung carcinoma type (SCLC, i.e. platinum-etoposide) is subject of debate. Recent molecular studies have identified two mutually exclusive genomic LCNEC subtypes, the co-mutated TP53 and RB1 (i.e. SCLC like) and the STK11/KEAP1 (predominantly RB1 wild-type, i.e. NSCLC like) subtype. We determined if genomic LCNEC subtypes are clinically relevant for chemotherapy (CT) outcome.

Methods: Clinical data and tumour specimens were retrospectively obtained from the Netherlands Cancer Registry and Pathology Registry (PALGA, 2003-2012). All first-line CT treated patients with panel-consensus diagnosed LCNEC were included for next-generation sequencing (NGS) analysis for TP53, RB1, STK11, and KEAP1 genes. Furthermore, immunohistochemistry for RB1 (pRB1, 13A10) was analysed (H-score, ≥50 considered as positive). NGS and pRB1 results were correlated with overall survival (OS) and progression free survival (PFS) by Kaplan Meier plots and Log-rank test.

Results: LCNEC was panel-consensus diagnosed in 148/232 patients; 79 passed quality control for NGS and 109 for pRB1. RB1 mutations were found in 47% (n = 37) and loss of pRB1 expression in 72% (n = 78) of the cases. Mutations in RB1 were mutually exclusive with mutations in STK11 (n = 8; P = 0.006). Due to reported resistance in neuroendocrine carcinomas, we analysed NSCLC-CT without pemetrexed-CT; OS was significantly longer for NSCLC-CT (n = 15, 9.6 [7.7-11.6] months) compared to SCLC-CT (n = 13, 5.8 [5.5-6.1] months, P = 0.026). LCNEC tumours expressing pRB1 also had longer OS when treated with NSCLC-CT (n = 14, 9.6 [7.4-11.8] vs. n = 9, 1.9 [1.7-2.1] months, P = 0.001). PFS of RB1 wild-type NSCLC-CT treated patients was significantly longer than SCLC-CT (P = 0.018) also for pRB1 (P = 0.023). In patients with a *RB1* mutation OS and PFS were not significantly different for NSCLC-CT vs. SCLC-CT.

Conclusions: In LCNEC with RB1 wild-type, NSCLC-CT correlates with a more favourable outcome compared to SCLC-CT. However, RB1 mutated LCNEC treated with NSCLC-CT have similar clinical outcomes as compared to SCLC-CT. Prospective studies should be initiated.

Legal entity responsible for the study: Maastricht University Medical Center

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432PD Prognostic impact of RNA expression profile (EP) in the phase III DECISION trial for patients with advanced radioactive-iodine refractory differentiated thyroid cancer (DTC)

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Background: Sorafenib has demonstrated a significant impact in progression free survival (PFS) in patients with advanced DTC in the DECISION trial. BRAF and RAS

Table: 432PD Clinical variables in each expression profiles

		BRAF like (n = 56)	RAS like (n = 28)	non-BRAF/RAS-like (n = 41)
Treatment	Sorafenib	37(66.1%)	9 (32%)	22 (53.7%)
	Placebo	19 (33.9%)	19 (68%)	19 (46.3%)
Sex	Female	26 (46.4%)	19 (68%)	15 (36.6%)
	Male	30 (53.6%)	9 (32%)	26 (63.4%)
ECOG	0	36 (64%)	15 (53.6%)	29 (70.7%)
	1-2	20 (36%)	13 (46.4%)	12 (29.3%)
Tumor histology	Papillary	53 (94.6%)	14 (50%)	6 (14.6%)
	Follicular	2 (3.6%)	7 (25%)	24(58.5%
	Poorly differentiated	1 (1.8%)	7 (25%)	10 (24.4%)
BRAF status	Mutated	31 (55.4%)	2 (7%)	0 (0%)
	Wild type	25 (44.6%)	26 (93%)	41 (100%)
RAS status	Mutated	5 (8.9%)	14 (50%)	1 (2.4%)
	Wild type	51 (91.1%)	14 (50%)	40 (97.6%)

mutation status (MS) have not shown prognostic significance on PFS and overall survival (OS) in multivariate model. The aim of this study was to correlate different RNA expression profiles with PFS and OS in a multivariate model.

Methods: We previously identified 3 expression profiles, BRAF, RAS and non-BRAF/RAS-like based on RNA-seq analysis (77 million paired-end reads for each sample on HiSeq2000) of 125 tumour samples of patients included in the DECISION trial. RNAseq reads were mapped against the human reference genome (GRCh38) with STAR (v2.5.1b) using ENCODE parameter. We used multivariate Cox proportional models to study the association between clinical variables (sex, age, thyroid cancer histology, Eastern Cooperative Oncology Group performance status), arm of treatment and biomarkers (EP and MS) with PFS and OS.

Results: The clinical variables in each expression profiles are shown in Table. Multivariable analysis indicated that only sorafenib treatment (HR: 0.39, 95% CI 0.23-0.66, $p < 0.001$), age (HR: 0.97, 95% IC 0.94-0.99, $p = 0{,}002$) and BRAF-like EP (HR = 0.41, 95% IC 0.17-0.99, $p = 0.046$) were independent prognostic factors for PFS. No significant prognostic factors we identified for OS. However, in papillary histology (PTC), only the BRAF-like EP was associated with outcome (HR = 0.32, 95% IC 0.118-0.876, $p = 0.026$).

Conclusions: RNA-seq analysis identifies 3 different expression profiles in DTC: BRAF-like, RAS-like and non-BRAF/RAS-like. BRAF-like EP includes almost all BRAF mutant tumors but also a 45% of tumors with no mutation in BRAF gene. In the multivariate analysis, BRAF-like EP has shown a better prognostic factor for PFS in DTC and for OS in PTC.

Legal entity responsible for the study: Vall d'Hebron Institute of Oncology

Funding: Bayer HealthCare Pharmaceuticals, Inc.

Disclosure: C. Peña: Bayer employee. All other authors have declared no conflicts of interest.

433PD Comprehensive genomic profiling of metastatic and relapsed thyroid gland carcinomas is associated with tumor type and reveals new routes to targeted therapies

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Background: We queried whether CGP could differentiate the mTC subtypes of papillary (PTC), follicular (FTC), medullary (MTC) and anaplastic (ATC) carcinomas and their potential responses to targeted and immunotherapies.

Methods: CGP was performed on FFPE samples using hybridization-captured, adaptor ligation based libraries to a mean coverage depth of > 500X for up to 315 cancer-related genes. Total mutational burden (TMB) was determined on 1.1 megabases of sequenced DNA as previously described (PMID: 28420421).

Results: 778 clinically advanced mTC were studied. Median age across the subtypes was similar with male patients slightly more frequent than females except for PTC. ATC had the highest median GA/sample at 4.34. *BRAF* was a target option for 73% of PTC and 39% of ATC, and *RET* for MTC in 81% of cases. Oncogenic rearrangements of *RET*, *BRAF*, *ALK*, and *NTRK1* were detected in 8%, 3%, 1%, and 1% of PTC cases, respectively, and in 1%, 1%, 0%, and 1% of ATC cases, respectively, but not detected in any cases of FTC or MTC. At 66%, *TP53* GA were most frequent in ATC. *TERT* GA were 58-67% in PTC, FTC and ATC and 0% in MTC. TMB was extremely low for all

Table: 433PD

	PTC	FTC	MTC	ATC
No. Patients	408	77	113	180
Median age (years)	59	60	54	64
Gender (F/M)	215/193	37/40	46/67	88/92
GA/tumor	2.75	3.01	1.96	4.34
Significant genes altered	*BRAF TERT TP53 RET*	*TERT NRAS TP53 PTEN HRAS*	*RET VHL MEN1 HRAS CCND1*	*TP53 TERT BRAF NRAS PIK3CA NF1 NF2 PTEN*
TP53 GA Frequency	11%	16%	2%	66%
RET GA Frequency	9%	0%	81%	2%
hTERT Frequency	58%	67%	1%	61%
BRAF GA Frequency	73%	7%	0%	39%
BRAF, RET, ALK, or NTRK rearrangemens	13%	0%	0%	3%
Total Mutational Burden ≥10 mut/Mb	2%	1%	2%	3%
Opportunity for Targeted Therapies	High (BRAF, oncogenic fusions)	Low	High (RET)	Moderate (BRAF, oncogenic fusions)

4 mTC tumor types with only 3 mTC (<1%) having ≥ 20 mut/Mb. Examples of mTC with responses to targeted therapies will be presented.

Conclusions: Refractory mTC patients are generally older than patients with classic localized primary PTC, and feature relatively more males. Advanced stage PTC, and to a lesser extent ATC, is frequently driven by *BRAF* GA or oncogenic rearrangements. Relapsed MTC is nearly universally driven by *RET* GA, whereas FTC has no dominant driver GA identified. TMB appears to be low for all subtypes of MTC, suggesting low potential for immunotherapies.

Legal entity responsible for the study: Jeffrey S. Ross

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434PD Impact of duration of dose interruption on the efficacy of lenvatinib (LEN) in a phase 3 sudy in patients (pts) with radioiodine refractory differentiated thyroid cancer (RR-DTC)

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Background: LEN prolonged progression-free survival (PFS) in pts with RR-DTC in the SELECT trial, and efficacy was maintained in all subgroups. Toxicity was manageable with dose modifications, but whether a longer period of dose interruption might impact the efficacy of LEN was unclear.

Methods: In SELECT, pts were randomized 2:1 to receive LEN 24 mg/day or placebo. Pts assigned to LEN were divided into 2 groups: pts with duration of dose interruption <10% (A) and pts with duration of dose interruption ≥10% (B) of total treatment duration. A and B were not randomized groups. PFS, objective response rate (ORR), and safety were analyzed in both groups.

Results: Of 261 LEN-treated pts, there were 134 in group A and 127 in group B. Differences in pt characteristics between groups (A and B) were, respectively: age (>65 years, 33% and 49%), race (Asian, 10% and 25%), and ECOG performance status (0, 64% and 46%). Median duration of dose interruption was 19 days (range: 0–63) and 61 days (range: 2–266) in groups A and B, respectively. Median PFS was not reached (hazard ratio [HR] to placebo: 0.14; 95% CI: 0.09–0.20, P < 0.001) in group A and 12.8 months (HR to placebo: 0.31, 95% CI: 0.22–0.43) in group B. ORR was 76% for group A and 53% for B. Disease control rate was 88% and 87% in groups A and B, respectively. Common adverse events (AEs) were similar in both groups, but incidences were different for diarrhea (A: 74%; B: 58%), decreased appetite (A: 45%; B: 62%), decreased weight (A: 57%; B: 44%), palmar-plantar erythrodysesthesia (A: 27%; B: 38%), and proteinuria (A: 23%; B: 42%). Common AEs leading to dose interruption or reduction included diarrhea (A: 24%; B: 21%), hypertension (A: 16%; B: 24%), proteinuria (A: 11%; B: 27%), and decreased appetite (A: 10%; B: 27%).

Conclusions: Longer duration of dose interruption may negatively affect the potential efficacy of LEN. Management of toxicities is essential to avoid long dose interruption. Differences in pt characteristics might confound the results. However, in this analysis LEN achieved improved PFS and ORR compared to placebo, regardless of length of dose interruption.

Clinical trial identification: NCT01321554

Legal entity responsible for the study: Eisai Inc

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436PD Preliminary safety and efficacy of rovalpituzumab tesirine in patients with delta-like protein 3-expressing advanced solid tumors

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Background: Delta-like protein 3 (DLL3) is an atypical Notch receptor family ligand expressed in high-grade neuroendocrine carcinomas (NECs), but not in normal tissue. Rovalpituzumab tesirine (Rova-T^{TM}) is an antibody-drug conjugate targeting DLL3. A Phase 1 study of Rova-T in small cell lung cancer showed encouraging antitumor activity in patients (pts) with DLL3 expression, and was well-tolerated[1]. Rova-T may also be active in other DLL3-expressing tumors.

Methods: This is a Phase 1/2, open-label, multicenter study (NCT02709889) to determine safety and tolerability of Rova-T in 8 cohorts: malignant melanoma, medullary thyroid cancer (MTC), glioblastoma (GBM), large cell NEC (LCNEC), neuroendocrine prostate cancer (NEPC), high-grade gastroenteropancreatic NEC (GEP NEC), other NEC and other solid tumors. Eligible adults have a histologically confirmed, DLL3-expressing, advanced solid tumor relapsed/refractory to standard therapy, and no prior exposure to a pyrrolobenzodiazepine-based drug. A 3 + 3 dose escalation is used in each cohort, at doses 0.2-0.4 mg/kg of Rova-T administered intravenously on Day 1 of each 42-day cycle, and proceeding until a maximum tolerated dose (MTD) is determined. A 2-stage design will be used for disease-specific expansion cohorts.

Results: As of 3 April 2017, 31 pts (2 melanoma, 2 MTC, 3 GBM, 3 LCNEC, 3 NEPC, 3 GEP NEC, 10 other NEC, 5 other solid tumor) have been treated (26 pts at 0.2 mg/kg, 5 pts at 0.3 mg/kg Rova-T). The MTD has not been reached. Twenty-six pts (84%) had an adverse event (AE), and only 3/31 pts (10%) had a Grade 3+ AE deemed to be related to Rova-T. Common AEs were fatigue (32%), nausea (29%), and constipation (23%). Four pts had serosal effusions, 2 (6%) of which were assessed to be drug-related, and 3 pts (10%) had adverse skin reactions. Ten pts (32%) discontinued treatment, 5 for progressive disease and 4 due to AEs. Eleven pts have had post-baseline tumor assessments, and anti-tumor activity has been observed in multiple disease cohorts.

Conclusions: Preliminary safety and efficacy data of Rova-T warrant continued study in these disease populations, and will be updated at time of presentation. 1. Rudin et al., Lancet Oncol 2016.

Clinical trial identification: NCT02709889

Legal entity responsible for the study: AbbVie Stemcentrx

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437PD Integrative DNA methylome and miRNA transcriptome analysis for new biomarker discovery in entero-pancreatic neuroendocrine tumours (EP-NETS)

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Background: Several attempts to improve the knowledge about the molecular biology of EP-NETS. However, the majority of these studies rely on alterations or pattern descriptions rather than integrative analysis of the findings derived from different platforms. We aim to identify new potential biomarkers integrating the differential expression of miRNAs and DNA methylated regions.

Methods: From a series of 115 EP-NETS formalin-fixed and paraffin embedded samples, we selected 8 cases of small intestine (SI) NETS and 8 pancreatic (P) NETS based on relapse (yes vs no) trying to identify the most phenotypically different cases within these groups in our series. DNA and RNA were extracted. The methylome *EPIC* array was used to determine differentially methylated regions (DMRs) and a transcriptomic array was used to analyse miRNA expression. Quality check (QC) of data was ran prior to analysis. False discovery rate (FDR) was applied to correct for multiple comparisons. Chromosomal regions with differentially expressed miRNAs and DMRs were plotted to perform an integrative analysis.

Results: Sample-wise and chip-wise QC were performed. DMRs were analyzed comparing patients with or without relapse (R) in SI-NETS and PNETS. The most significant differentially methylated regions for R vs non-R in PNETS were found in chromosome (chr) 2, and in chr 1 and 2 for SI-NETS. A gene set analysis of the DMRs was performed using a FDR < 0.1. Gene sets commonly represented in SI-NETS and PNETS are within CD8 TCR pathway and endothelin pathway. None of the miRNAs maintain significance using a FDR <0.2. However, one of the top10 differentially expressed miRNAs for PNETS, hsa-miR-149-5p (uncorrected $p = 0{,}014$) is found in the same region of the chr 2 were the most significant DMRs and differentially methylated promoters are located. Has-miR-9-1-5p (uncorrected $p = 0.017$) was also differentially expressed in PNETs and located close to one of significant DMRs in chr 1.

Conclusions: It is feasible to integrate the analysis of DMRs and miRNAs in EP-NETS. Certain areas of chr1 and 2 concentrated regions with different epigenetic regulation when compare R vs non-R. Validation of the findings is ongoing.

Legal entity responsible for the study: IdIPAZ - Hospital Universitario La Paz

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Disclosure: All authors have declared no conflicts of interest.

438PD Improved time to quality of life deterioration in patients with progressive midgut neuroendocrine tumors treated with 177Lu-DOTATATE: The NETTER-1 phase III trial

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Background: Neuroendocrine tumor (NET) progression is associated with deterioration in quality of life (QoL). We assessed the impact of ^{177}Lu-DOTATATE treatment on the time to clinically relevant change (deterioration) in health-related QoL (HRQoL). The NETTER-1 trial is an international phase III study in patients with progressive, somatostatin receptor positive midgut NET. Patients were randomized to receive treatment with ^{177}Lu-DOTATATE versus high-dose (60 mg) Octreotide LAR (Oct). EORTC questionnaires QLQC-30 and G.I.NET-21 were assessed during the trial to determine the impact of treatment on HRQoL.

Methods: 231 patients completed EORTC QLQC-30 and G.I.NET-21 questionnaires at baseline and every 12 weeks thereafter until tumor progression centrally confirmed. QoL scores were converted to a 100-point scale according to EORTC instructions and individual changes from baseline scores were assessed. Time to QoL deterioration (TTD) was defined as the time from randomization to the first QoL deterioration $\geq$10 points for each patient in the corresponding domain scale. This magnitude of variation was considered clinically relevant. All analyses were conducted on the ITT population.

Results: TTD was significantly longer in the ^{177}Lu-DOTATATE arm ($N = 117$) vs the control arm ($N = 114$) for the following domains: global health status (hazard ratio (HR) 0.406; $p = 0.0006$), physical functioning (HR 0.518; $p = 0.0147$), role functioning (HR 0.580; $p = 0.0298$), fatigue (HR 0.621; $p = 0.0297$), pain (HR 0.566; $p = 0.0247$), diarrhea (HR 0.473; $p = 0.0107$), disease related worries (HR 0.572; $p = 0.0176$) and body image (HR 0.425; $p = 0.0058$). In the other domains TTD did not reach statistical significance between the arms. Differences in median TTD were clinically significant in several domains: 28.8 months vs. 6.1 months for global health status, and 25.2 months vs. 11.5 months for physical functioning.

Conclusions: This analysis from the NETTER-1 Phase III study demonstrates that ^{177}Lu-DOTATATE provides a significant quality of life benefit for patients with progressive midgut NETs compared to high-dose octreotide, in addition to the meaningful increase in progression-free survival already reported.

Clinical trial identification: NCT01578239

Legal entity responsible for the study: NETTER-1 study group and Advanced Accelerator Applications

Funding: Advanced Accelerator Applications

Disclosure: M. Lopera Sierra: Advanced Accelerator Applications Chief Medical Officer E. Krenning: Stock ownership. All other authors have declared no conflicts of interest.

439PD Peptide receptor radionuclide therapy of neuroendocrine neoplasms using lutetium-177 and yttrium-90 labeled somatostatin analogs: A single center experience in over 1000 patients

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Background: Peptide receptor radionuclide therapy (PRRT) of patients with somatostatin receptor expressing gastroenteropancreatic neuroendcrine neoplasms (NEN) has shown promising results in a recently published clinical trial (NETTER-1, NEJM, Jan 2017). In this study, we performed an intention to treat analysis in over 1000 patients with NEN (pancreas, mid-gut, lung and others) treated at our center.

Methods: From 2004, 1048 patients received at least one cycle of Yttrium-90 or Lutetium-177 based PRRT, and were included in an intention to treat analysis. Ga-68 somatostatin receptor (SSR) PET/CT was used for restaging and response to therapy assessment (EORTC criteria). Accordingly, overall survival (OS) and progression free survival (PFS) were calculated. Adverse events (hematotoxicity and nephrotoxicity) were determined by CTCAE (v4.03).

Results: Overall survival (95% CI) was 51 months (47.0-54.9) and differed according to tumor grade, location of primary tumor, functionality, previous therapies, and the radioisotope used for PRRT. PFS was 19 months (16.9-21.0), which was influenced by tumor grade, location of primary tumor, and the radioisotope used for PRRT. PFS after initial progression and first and second resumption of PRRT, following therapy-free intervals of $>$ 6 months, was 11 months (9.4-12.5) and 8 months (6.4-9.5), respectively. Myelodysplastic syndrome or leukemia developed in 2.1% patients. No grade 4 nephrotoxicity was observed with Lu-177. Few patients with severe renal dysfunction before PRRT, progressed to end-stage renal disease. No patient with normal renal function before PRRT developed G3 (or higher) nephrotoxicity.

Conclusions: PRRT is effective as it favorably prolongs the OS and PFS in patients with metastatic neuroendocrine neoplasms. However, this depends on the tumor grade, location of primary tumor, and the radionuclide used for therapy. Low rate of severe hematotoxicity were observed. There was no therapy associated severe nephrotoxicity in patients with normal renal function prior to commencement of PRRT.

Legal entity responsible for the study: Richard P. Baum

Funding: None

Disclosure: All authors have declared no conflicts of interest.

440PD Efficacy and safety of telotristat ethyl in patients with carcinoid syndrome inadequately controlled by somatostatin analogs: Analysis of the completed TELESTAR extension period

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Background: The phase III, placebo-controlled, randomized TELESTAR study evaluated efficacy and safety of telotristat ethyl (TE) in patients (pts) with diarrhea (≥4 bowel movements [BMs]/day) due to carcinoid syndrome (CS) inadequately controlled by somatostatin analogs (SSAs). TE, a tryptophan hydroxylase inhibitor, decreases peripheral serotonin levels. As add-on treatment to SSAs, TE 250 mg 3x/day (tid) and TE 500 mg tid significantly reduced BM frequency ($p < 0.001$) compared with placebo over the 12-week Double-blind Treatment (DBT) period. After Week 12, pts crossed over to a 36-week Open-label Extension (OLE) period with TE 500 mg tid; data from the full 48 weeks are presented.

Methods: Changes from baseline in BM frequency (monitored weekly), urinary 5-hydroxyindoleacetic acid (u5-HIAA; Weeks 18, 24, and 48), European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) score (Weeks 24 and 48), and safety during the OLE period were evaluated.

Results: Of the 135 pts randomly assigned, 118 completed the DBT period; 115 pts subsequently entered (and 79 completed) the OLE period. Of the 36 pts who discontinued the OLE period, the most frequent reasons were adverse event (AE; 15 pts) and withdrawal of consent (9 pts). Treatment-emergent AEs led 18 pts to discontinue TE; gastrointestinal disorder was the most commonly reported reason (6 pts). Reductions from baseline in BM frequency (~2 BMs/day) and u5-HIAA levels (range –20.0 mg to –49.5 mg/24 hours) during the OLE were consistent with results of the DBT period and persisted through Week 48. Improvement in EORTC QLQ-C30 diarrhea subscale scores relative to baseline (range –18.8 to –30.6 points) was notable and persisted through Week 48. Crossover into the OLE period was well tolerated. Treatment-emergent AEs were mainly mild to moderate and occurred at a similar rate as in the DBT period.

Conclusions: Patients benefitted from TE throughout the OLE period. TE was well tolerated over 48 weeks and its efficacy was consistent with previously reported data.

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Legal entity responsible for the study: Lexicon Pharmaceuticals, Inc.

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441PD Follow-up recommendations for completely resected gastroenteropancreatic neuroendocrine tumours (GEP-NETs): Consensus guidelines from the Commonwealth NET collaboration (CommNETs) in conjunction with the North American NET Society (NANETS)

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Background: NETs are uncommon, and there is no consensus regarding the optimal follow-up frequency or modality after resection. Current follow-up guidelines for resected GEP-NETs are based on limited evidence and our large, international practice survey showed poor compliance by NET expert clinicians. A need for clear and practical guidelines was identified.

Methods: A RAND/UCLA appropriateness process was employed given the lack of published data. A systematic review was undertaken as well as a multi-national practice survey to understand current follow-up patterns. Results from two large retrospective reviews (Ontario, Canada and Tampa, Florida) examining outcome following curative surgery were obtained. An 18-member multidisciplinary international panel scored 193 clinical scenarios for appropriateness of timing of consultations and investigations for detecting recurrence on a 1-9 scale. At a face-to-face consensus conference, the final follow-up recommendations were developed.

Results: Twelve studies were identified describing follow-up strategies post-resection, with only one comparing follow-up strategies. Data from our practice survey ($n = 163$) and our population-based study ($n = 936$) are separately reported. Based on the scenario scoring, the panel resolved 14 summary statements, with the major themes of (1) less frequent follow up visits and investigations within the first five years (2) longer follow up even beyond 10 years (3) different recommendations for pancreatic versus gastrointestinal NETs (4) identification of low risk subgroups where no routine follow-up was recommended (5) no role for any serum or urine biomarkers, or chest imaging (6) the need to evaluate functional imaging in follow-up.

Conclusions: Streamlined, practical guidelines were developed for the follow-up of patients with resected GEP-NETs. These guidelines differ significantly from other current guidelines. The expert consensus was informed by previously unavailable large outcome datasets. Compliance, cost-effectiveness and patient acceptability will be evaluated in future studies.

Legal entity responsible for the study: Sunnybrook Research Institute

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442P Long-term survival of patients with carcinoid syndrome in clinical trials of telotristat ethyl

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Background: Patients with carcinoid syndrome (CS) in the setting of metastatic neuroendocrine tumors (NETs) experience considerable morbidity and mortality. From the time of diagnosis of metastatic NETs, median survival has been estimated to be approximately 31–75 months. CS is associated with tumoral secretion of serotonin and subsequent debilitating diarrhea, which poses a significant health risk. In previous studies, telotristat ethyl (TE), a tryptophan hydroxylase inhibitor, was effective and well tolerated in treating CS diarrhea. At enrollment, patients in these studies had already survived an average of 6–8 years with metastatic NETs since their initial diagnoses.

Methods: Adverse events reported during treatment with TE were pooled from 2 Phase 2 and 3 Phase 3 clinical trials of TE in patients with CS. The long-term safety of TE was examined, causes of hospitalization and death were reviewed, and an estimate of overall survival was obtained.

Results: A total of 239 patients with CS received treatment with TE in Phase 2 and 3 clinical trials. For these patients, as of the end of 2016, the mean duration of exposure was 1.3 years, and maximum 5.7 years. The leading causes of hospitalization were gastrointestinal disorders and surgical and medical procedures, mostly attributable to the underlying tumor and related treatment. Survival estimates at 1, 2, and 3 years were 93%, 88%, and 77%, respectively. Nearly all deaths were due to progression or complication of the underlying disease, and none were attributable to TE. There was 1 death in Year 4 and no deaths in Years 5 and 6 of patient follow-up in this data set. The median survival with TE was not reached at the end of the 6-year Follow-up period.

Conclusions: Our review of the long-term safety data for TE indicates that patients with CS treated with TE in Phase 2 and 3 studies experienced encouraging survival rates.

Clinical trial identification: NCT02026063, NCT02063659, NCT01677910, NCT01104415, NCT00853047

Legal entity responsible for the study: Lexicon Pharmaceuticals, Inc.

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443P Identifying symptom and quality of life improvements in patients with carcinoid syndrome treated with telotristat ethyl: Qualitative patient exit interviews from the TELESTAR Trial

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Background: Carcinoid syndrome (CS) is a rare condition in patients (pts) with neuroendocrine tumors (NETs), characterized by diarrhea, flushing, and abdominal pain that impact health-related quality of life (HRQoL). We assessed symptoms and HRQoL in pts with inadequately-controlled CS enrolled in TELESTAR (NCT01677910).

Methods: English or German-speaking pts randomized 1:1:1 to 12 wks of double-blinded (DB) treatment with telotristat ethyl (TE) 250mg, 500mg, placebo were invited to a blinded, qualitative, semi-structured exit interview after the DB period to assess symptoms, HRQoL concepts (improved/not changed/worsened), and TE treatment effects. Concepts were freely reported by pts and not solicited. EORTC QLQ-C30 and GINET21 questionnaires assessed HRQoL, daily diaries assessed baseline (BL) bowel movement (BM) frequency. Analyses compared pts with durable response (DRs; predefined as BM frequency reduction of $\geq$ 30% from BL for $\geq$50% of DB period) and without durable response.

Results: TELESTAR enrolled 135 pts, 45 per group; 34 pts (9, 16, 9 in TE 250mg, 500mg, placebo, respectively), including 10 DRs consented to interviews. BL age, gender, race, BMs/wk of interviewed pts (IPs) were similar to non-interviewed pts. Most qualitative concepts were captured, to an extent, by the QLQ-C30; most common HRQoL qualitative concepts identified were daily life activities, physical, and psychological, with most TE-treated pts improving in these over the DB period. The most common symptoms (improvement/no change) reported in all IPs were diarrhea consistency (n = 17/n=10), frequency (n = 17/n=9), urgency (n = 11/n=7); flushing (n = 11/n=7), and fatigue (n = 9/n=4). A higher proportion of TE-treated pts and DRs reported symptom and HRQoL concept improvements. Durable response ($p < 0.001$) and treatment satisfaction ($p = 0.0137$) correlated with diarrhea QLQ-C30, but no other QLQ-C30/GINET21 scores.

Conclusions: The QLQ-C30 covered most qualitative concepts, but due to the lack of emphasis on key symptoms, may not adequately reflect pt perspectives. Interviews suggested improvements in symptoms and HRQoL with TE treatment and in DRs.

Clinical trial identification: NCT01677910

Legal entity responsible for the study: Lexicon Pharmaceuticals

Funding: Lexicon Pharmaceuticals and Ipsen Pharma SAS

Disclosure: F. Marteau, M. Feuilly: Employee of Ipsen. P. Williams, B. Arnould: Employee of Mapi.

444P Carcinoid syndrome: Patient outcomes from a European Neuroendocrine Tumour Society (ENETs) centre of excellence

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Background: Carcinoid syndrome (CS), characterised by flushing, diarrhoea, wheeze and fibrotic valvulopathy, arises in patients (pts) with advanced NETs due to serotonin and kallikrein secretion.

Methods: Sequential pts with advanced well-differentiated gastroenteropancreatic NETs (GEP-NETs) treated at The Christie (1998-2017) with $\geq$1 carcinoid symptom(s) and raised serum/urinary 5-hydroxyindoleacetic acid (5-HIAA) were identified. Ratio of 5-HIAA/upper limit normal (ULN) was calculated. Progression-free (PFS) and overall survival (OS) were estimated (Kaplan-Meier method) and prognostic factors identified (Cox proportional hazards model).

Results: Of 882 pts, 139 (16%) had CS: median (med) age 64 yrs, 55% male, 80% performance status (PS) 0-1, 13% PS 2; 65% had small bowel primary, 10% large bowel, 4% pancreas, 0.7% gastric, 21% unknown primary (consistent with GEP-NET origin). Tumour grade (G) was 1 in 45%; G2 in 29%; symptoms included diarrhoea (91%), flushing (89%), wheeze (22%), and carcinoid heart disease (CHD; 35%). Fifty-seven (41%) had primary resection, and 121 (87%) had liver metastases. In first line, 66% received a somatostatin analogue (SSA), 20% debulking surgery, 14% other. Med baseline 5-HIAA levels were 8.45 x ULN (urinary: 10.56 x ULN, serum: 6.07 x ULN). Med follow-up was 45.7 months (mo). Med PFS and OS were 27.0 (95%CI 17.2-33.9) and 65.4 (95%CI 50.4-76.4) mo. On univariate analysis, small bowel primary ($P = 0.045$), liver metastases ($P = 0.03$), Ki-67 ($P < 0.01$) and 5-HIAA baseline ratio ($P < 0.001$) were prognostic for PFS; and age ($P < 0.01$), PS ($P < 0.01$), primary in situ ($P < 0.001$), CHD ($P = 0.03$), Ki-67 ($P = 0.03$), baseline 5-HIAA ratio ($P < 0.001$) and use of SSA vs surgery ($P = 0.02$) were prognostic for OS. On multivariable analysis, high Ki-67 (HR 1.06, 95%CI 1.00-1.12, $P = 0.049$) and baseline 5-HIAA ratio (HR 1.03, 95%CI 1.01-1.05, $P = 0.001$) were prognostic for worse PFS. Primary in situ (HR 2.23, 95%CI 1.09-4.54, $P = 0.03$) and high baseline 5-HIAA ratio (HR 1.02, 95%CI 1.00-1.04, $P = 0.04$) were prognostic for worse OS. Change in 5-HIAA at 6 mo was not prognostic for PFS ($P = 0.42$) or OS ($P = 0.60$).

Conclusions: Baseline 5-HIAA ratio, but not change from baseline to 6 months, was prognostic for PFS and OS. Treatment optimisation is pivotal.

Legal entity responsible for the study: Audit Department - The Christie NHS Foundation Trust, Manchester

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Disclosure: All authors have declared no conflicts of interest.

445P Relationship between symptoms and health-related quality of life benefits in patients with carcinoid syndrome: Post-hoc analyses from TELESTAR

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Background: The safety and efficacy of telotristat ethyl (TE) in patients (pts) with metastatic neuroendocrine tumors (NETs) and carcinoid syndrome (CS) not adequately controlled with somatostatin analogs (SSAs) have been demonstrated. TE-treated pts showed significantly greater reductions in bowel movement (BM) frequency and more presented with durable response than placebo (PBO)-treated pts. These post-hoc analyses examined the relationship between improvements in symptoms and health-related quality of life (HRQoL) in pts who were durable responders (DRs; n = 48) and non-durable responders (NDRs; n = 87), irrespective of treatment group, in TELESTAR (NCT01677910).

Methods: Pts were randomized 1:1:1 to TE 250mg, 500mg, and PBO three times daily during the 12-week (wk) double-blind (DB) treatment period; durable response was predefined as a daily BM frequency reduction of $\geq$ 30% from baseline for $\geq$50% of the DB period. Clinical symptoms were assessed via daily records, HRQoL by the EORTC QLQ-C30 and QLQ-GINET21 questionnaires. The difference in arithmetic means and associated 95% CIs were used as a descriptive measure of group effects.

Results: 135 pts were randomized, 45 in each group. The mean difference [95% CI] in change from baseline between DRs and NDRs at Wk12 was (1.8 [-2.3, -1.2]) for daily BM frequency, (-1.2 [-1.6, -0.7]) for daily flushing, (-38.7 [-70.0, -7.3] mg/24 hrs) for u5-HIAA levels, (-1.2 [-1.8, -0.6]) for abdominal pain severity and (-0.3 [-0.4, -0.2]) for urgency to defecate. DRs showed meaningful and/or significant improvements in QLQ-C30 global health (8.1 [-0.3, 16.5]), summary score (4.9 [0.6, 9.2]), social

functioning (5.1 [-4.7, 14.9]), nausea/vomiting (-7.5 [-15.4, 0.4]), pain (-16.0 [-27.0, -5.0]), dyspnea (-5.7 [-15.5, 4.1]), diarrhea (-14.7 [-26.5, -2.9]), and GINET21 gastrointestinal symptoms (-9.3 [-16.3, -2.2]) versus NDRs.

Conclusions: Durable response was associated with reductions in the symptoms and overall clinical burden of CS. DRs showed significant and/or meaningful improvements in global HRQoL, nausea, pain, diarrhea, and gastrointestinal symptoms.

Clinical trial identification: NCT01677910

Legal entity responsible for the study: Lexicon Pharmaceuticals

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Disclosure: M. Pavel: Consulting fees and honoaria from Ipsen, Lexicon Pharmaceuticals, Novartis, Pfizer. D. Cella: Consulting fees and research grants from Bayer, BMS, Ipsen, Novartis, Pfizer. J.L. Beaumont: Consulting fees from Novartis. F. Marteau, M. Feuilly, S. Gabriel, A. Houchard: Employee of Ipsen. J. Ramage: Speaker's fees from Ipsen, Novartis, Pfizer; Research grants from IEL, Ipsen, Novartis, Pfizer. D. Hörsch: Consulting and/or honoraria and/or advisory boards from Ipsen, Lexicon Pharmaceuticals, Novartis, Pfizer; Research grants from Ipsen, Novartis, Pfizer. M.H. Kulke: Consulting fees from Ipsen, Lexicon Pharmaceuticals. All other authors have declared no conflicts of interest.

446P Benefit of oral monotherapy with pazopanib in metastatic gastroenteropancreatic neuroendocrine tumours

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Background: Although standard therapy for gastroenteropancreatic neuroendocrine tumors (GEP-NETs) can provide symptom relief and delay tumour progression, new strategies are needed for patients with metastatic disease. The aim of this study was to investigate the antitumour activity and safety profile of pazopanib - a selective multitargeted receptor tyrosine kinase inhibitor of vascular endothelial growth factor receptor and platelet-derived growth factor receptor.

Methods: We enrolled 124 patients with metastatic GEP-NETs. Pazopanib was administered orally at a dose of 800 mg daily with a 28-day cycle. The primary endpoint was overall response rate (ORR) according to Response Evaluation Criteria in Solid Tumors. The secondary endpoints were overall survival (OS), progression-free survival (PFS) at 6 months and safety profile of pazopanib (general tolerability and toxicity). The third endpoint was to compare the clinicopathological features of tumours and biomarker analysis with survival of the patients.

Results: The mean follow-up time was 196±87 days with a range of 67-268 days; 26 patients died within the observation time. 69% of the patients had confirmed pancreatic GEP-NET and 51% had colorectal, gastric and duodenal GEP-NET. 59 (47.6%) patients had G1, 34 (27.4%) G2 and 31 (25%) had G3 GEP-NET. ORR was 24% (19 of 124 patients), stable disease was achieved in 49 patients (39.5%) and PFS at 6 months was 36%. Median OS was 10.2 months (95% CI, 5.4-13.2 months). The most common grade 3-4 adverse events attributed to therapy were neutropenia (11%), proteinuria (14%), diarrhea (7%), and fatigue (12%). Patients with high CgA levels had the highest mortality risk (hazard ratio 3.478, 94% confidence interval 1.313-4.727, $p < 0.001$) and worse outcomes. Furthermore, extremely high CgA levels (>3000 ng/mL, range 8300-800 ng/mL) were associated with low survival independently from the Ki-67 score in a multivariate Cox regression model.

Conclusions: Pazopanib demonstrated a comparable therapeutic efficiency as well as a satisfying safety profile compared to other targeted agents in the treatment of patients with metastatic GEP-NETs.

Legal entity responsible for the study: Faculty of Medicine Osijek

Funding: Faculty of Medicine Osijek

Disclosure: All authors have declared no conflicts of interest.

447P High hepatic tumor burden and cardiovascular comorbidities linked to carcinoid heart disease

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Background: One of the most common functioning syndromes associated with neuroendocrine tumors (NET) is the carcinoid syndrome (CS). By releasing vasoactive substances, these tumors can cause fibrotic complications, including right-sided valve heart fibrosis, named carcinoid heart disease (CHD). Factors associated with the onset and progression of CHD are poorly understood. We aimed to investigate prognostic factors associated with CHD.

Methods: Retrospective study of consecutive patients (pts) with advanced NET and CS and/or elevated 24h-urinary 5HIAA who performed an echocardiogram to screen for CHD. CHD was defined as echocardiographic evidence of moderate to severe tricuspid or pulmonar regurgitation.

Results: From 2009 to 2017 42 pts were included: Median age was 54.4 (19 – 85) years, 24 were female, 69% had midgut NET. The frequency of CHD was 38% (16 pts) CHD was not associated with age ($p = 0.79$), sex ($p = 0.38$), bone metastasis ($p = 0.66$), flushing ($p = 0.14$) or diarrhea ($p = 0.53$); the median urinary level of 5HIAA at diagnosis of CHD was numerically higher, albeit not significant, among CHD pts ($p = 0.20$). CHD was significantly associated with higher volume (>50% of parenchyma) of liver metastases [OR 13.86 (2.57 – 74.68), $p = 0.002$]. Time from symptoms to diagnosis of NET was borderline significant ($p = 0.08$). When CHD was defined as at least mild valve regurgitation, the frequency of CHD was 45% (19 patients) and we observed a significant association between the presence of cardiovascular comorbidities and CHD [OR 6.58 (1.09; 39.78), $p = 0.040$].

Conclusions: CHD is highly frequent among pts with CS. We found that high liver tumor burden and possibly, longer time of symptoms until diagnosis of NET were associated with CHD. Such findings probably imply that a delayed diagnosis negatively affects CS patients, increasing the risk of CHD. Interestingly, we found that concurrent cardiovascular disease was associated with CHD, as a potential predisposing factor.

Legal entity responsible for the study: Instituto do Câncer do Estado de São Paulo

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Disclosure: All authors have declared no conflicts of interest.

448P Bone metastases in patients with neuroendocrine neoplasms: A survey of natural history and clinical management

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Background: Bone metastases (BM) in neuroendocrine neoplasms (NEN) represent a poorly defined issue.

Methods: This is a nationwide survey among Italian institutions dealing with NEN patients. Characteristics of BM, clinical management, skeletal related events (SREs) and disease outcome were recorded.

Results: We analysed 321 patients with histological diagnosis of NEN and BM collected from 18 Italian Centers. Mean age was 59 y.o. (range 13-86). Primary sites were 47% gastroenteropancreatic (GEP), 36% lung, 4% Paraganglioma/Pheocromocytoma (Par/Pheo), 7% unknown, 5% others. The vast majority (72%) of NEN were already metastatic at diagnosis and the liver represented the second most frequent site of metastasis (in 77% of patients) during follow-up, in addition to BM. Bone was the first metastatic site in 41% of cases. Neoplasms were low/intermediate grade in 80% and high grade in 20%. SREs occurred in 32% of cases, mainly in lung and others. Median time to SRE was 4 months. It strictly correlated with the high grade, irrespective of the primary site. Bisphosphonates were administered in 32% of patients. Median survival from BM diagnosis was 65 months (range 45-78) in the whole population, with Par/Pheo at the best and high grade GEP at the worst limit. SRE, high grade (or in alternative high Ki-67) and prior lung metastases resulted significantly associated with worse overall survival at the multivariable analysis. After adjustment for tumor grade, survival of patients with GEP and lung NENs were similar.

Conclusions: This is one of the largest series of NEN patients with BM reported so far. This survey mirrors the Italian real clinical practice in this setting, as it included most Centers involved in NET patients' management. It showed that overall, BM from NEN are associated with a relatively long survival. Bisphosphonates were used in a low percentage of cases, probably related to SRE. Tumor grade confirmed its value in separating two survival categories, irrespective of primary site. The results of this analysis generated hypotheses for prospective trials in homogeneous clinical settings.

Legal entity responsible for the study: Nicola Fazio

Funding: None

Disclosure: All authors have declared no conflicts of interest.

449P Financial toxicity in patients with neuroendocrine tumors: Impact of a chronic disease on patients' economic situation

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Background: The diagnosis of cancer imposes physical, emotional and financial burdens on patients. So far, the socio-economic impact of cancer for patients in Germany is poorly understood. The aim of the project is to provide an overview on patients' financial losses due to a neuroendocrine tumor (NET) diagnosis as well as possible psychosocial effects.

Methods: This prospective quantitative study recruited n = 123 patients with NET from November 2016 to March 2017 at the National Center for Tumor Diseases, University Hospital Heidelberg. They completed a survey on patients' income, cancer-related out-of-pocket costs, disease burden (Distress Thermometer), quality of life (EORTC-LQ 29/30), health status (EQ-5D) and demographic data.

Results: 78.0% (n = 96) of the patients stated to have higher out-of-pocket costs because of their disease, mostly in terms of travel expenses and co-payments for medication. With regard to loss of income, 29.3% (n = 36) of the participants reported a minus, which is beyond 800€per month in almost half (44.4%) of these cases. 61.5% of the persons affected by income losses cannot compensate these by savings or credits. 33.3% (n = 41) of the responding patients indicated that they have to cut back on their expenses of daily living as a result of their disease. Higher cancer-related out-of-pocket costs per month were associated with lower estimation of patient's quality of life (p = 0.003), lower self-reported health status (p = 0.013) and a more severe perception of disease burden (p = 0.036) whereas a higher monthly income was strongly correlated with better quality of life (p=.008)/health status (p = 0.008) and lower disease burden (p = 0.006).

Conclusions: Given the fact that the majority of surveyed patients has to face financial losses due to their cancer diagnosis which is accompanied by the experience of distress as well as worsened quality of life and health status, there is a need for targeted measures that could prevent financial problems and reduce emotional burdens. Further research is required to address this aim.

Clinical trial identification: The trial was approved by the Instituional Research Ethics Committee (approval S-458/2016).

Legal entity responsible for the study: National Center for Tumor Diseases, University Hospital Heidelberg

Funding: Ipsen Pharma GmbH

Disclosure: All authors have declared no conflicts of interest.

450P Pancreatic exocrine insufficiency (PEI) in patients (pts) with well-differentiated neuroendocrine tumours (wd-NETs) treated with somatostatin analogues (SSAs): Incidence and impact on quality of life

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Background: Advanced wd-NET patients (pts) are commonly treated with SSAs. PEI may be under-estimated in trials due to difficulties in distinguishing carcinoid syndrome-related diarrhoea and PEI.

Methods: In this single-institution, prospective, observational study, sequential pts with advanced wd-NET were commenced on SSAs and followed for a minimum of 12 months (or until disease progression). Toxicity was prospectively assessed monthly. Faecal elastase testing (FE) (for diagnosis of PEI) and quality of life (QoL) questionnaires (QLQ-C30 and QLQ-GI.NET21) were performed 3-monthly.

Results: Of 52 pts recruited (Jan 15-Apr 16), 50 were eligible: median age 65.8 yrs; 58% male; ECOG performance status 0 (42%), 1 (46%) or 2 (12%); primary: small bowel (60%), pancreas (22%), lung (12%) and other (6%). Baseline median Ki-67 was 3.1% (range 0.7-25), serum 5HIAA: 195 nmol/L (95%CI 145-318) and chromogranin A (CgA): 327 ng/mL (95%CI 140-582). Most pts were metastatic (92%), non-functional (66%) and started SSA first-line (88%); depot SSA was octreotide in 60%, lanreotide in 40%. Forty-one pts (82%) started full-dose SSA (4-weekly octreotide 30mg or lanreotide 120mg); 96% achieved full dose; 3 pts required dose reduction due to toxicities. Grade (G) 1-2 toxicities were flatulence (50%), abdominal pain (32%), diarrhoea (30%), fatigue (20%), PEI (22%), nausea (16%), hyperglycaemia (6%), anorexia (4%) and constipation (2%). G 3-4 toxicities were few (G3 hyperglycaemia (n = 1) and G3 PEI (n = 1); no G4). Twelve pts (24%) developed SSA-related PEI (4 clinical diagnosis, 8 FE-confirmed) at a median of 2.9 mo (95%CI 1.7-8.6) after starting SSA; 11/12 (92%) pts received enzyme replacement. Questionnaires identified fatigue, insomnia and diarrhoea as the most important baseline symptoms; SSA therapy did not negatively-affect QoL. Estimated median progression-free survival (PFS) was 29.9 mo (95%CI 21.4-not reached). High baseline CgA was an independent factor for shorter PFS (HR 1.01 (95%CI 1.001-1.1); p-value 0.001) after adjustment for other factors (baseline 5HIAA, Ki-67).

Conclusions: SSA-induced PEI occurs in 1:4 pts; clinicians should actively identify and treat.

Legal entity responsible for the study: N/A

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Disclosure: All authors have declared no conflicts of interest.

451P Final analysis of time to subsequent disease progression/death in patients with metastatic enteropancreatic neuroendocrine tumours progressing under placebo and switched to lanreotide autogel/depot 120mg in the CLARINET open-label extension

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Background: The CLARINET core study established the antitumour activity of lanreotide Autogel 120mg/28 days (LAN) in metastatic enteropancreatic neuroendocrine tumours (NETs). The vast majority of the core study population (96%) had stable disease (SD) at baseline, but the LAN open-label extension (OLE) also included patients with progressive disease (PD; while receiving placebo [PBO] in the core study). Here, we report the final analysis of time to subsequent death/PD for patients with PD switched to LAN.

Methods: In the core study, patients with metastatic well-/moderately differentiated non-functioning enteropancreatic NETs received LAN/PBO for 96 weeks or until death/PD (RECIST 1.0). Eligible patients for the OLE (NCT00842348) had SD at core-study end or PD (with PBO only) during the core study. Adverse events (AEs) were recorded at 4-weekly visits. CT/MRI scans from OLE baseline (week 1) and every 24 weeks subsequently were assessed locally for PD (RECIST 1.0). Primary objective: long-term safety. Secondary objective: long-term efficacy, with assessments including PFS and time to subsequent death/PD (from Kaplan–Meier analyses; months approximated as 4 weeks).

Results: 89 patients were treated in both core and OLE studies (42 LAN–LAN [SD, n = 41]; 47 PBO–LAN [SD, n = 15]); 40% of the LAN–LAN vs. 47% of the PBO–LAN group had treatment-related AEs. Overall median LAN PFS, based on the intent-to-treat population (n = 101), was 38.5 months. Seven PD events (no deaths) occurred during the OLE in 15 patients entering with SD from the PBO arm of core study. In total, 32 patients with PD whilst receiving PBO in the core study entered OLE (of 59 potentially eligible); NETs were in pancreas in 17 patients, midgut in 10, hindgut in one, and of other/unknown origin in four. Of these patients, 20 had subsequent PD during the OLE and three died; median time to subsequent death/PD was 19.0 months [95% CI: 10.1; 26.7].

Conclusions: The final analysis of the CLARINET OLE study suggests benefit with LAN in patients who had experienced PD when receiving no NET-specific treatment (PBO), with median time to subsequent death/PD of 19 months.

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Legal entity responsible for the study: Ipsen Pharma

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452P Temozolomide-capecitabine (TemCap) chemotherapy for neuroendocrine neoplasms (NENs): Time to maximum response and optimal treatment duration

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Background: TemCap is an option for treatment of NENs; benefit of treatment until progression rather than a fixed 6-month (mo) course remains unclear.

Methods: Patients (pts) diagnosed with advanced NEN (pathology-confirmed), treated with TemCap with follow-up and available radiological response data were eligible for this retrospective study. Efficacy was assessed by RECIST v1.1.

Results: Of 62 pts identified (Jan'12-Jan'17), 60 were eligible. Median (med) age at starting TemCap was 63.6 yrs; 50% were male; Performance Status (PS) 0-1 (83.3%), 2 (16.7%); with NEN of lung (33.3%), pancreas (21.7%), small bowel (16.7%), colorectal (3.3%) and other (25.0%) origin. The med Ki-67 was 12% (range 1-29); most (83.3%) were well-differentiated [grade (G)1/typical (18.3%); G2/atypical (65%); G3 (16.7%)], non-functional (75.0%) and metastatic (90.0%). Pts received TemCap as first- (33.3%) or second- (35.0%) line, for a med of 5.58 mo (95%CI 5.33-5.78). After 6 cycles, 38 pts (63.3%) were progression-free (i.e. eligible for maintenance TemCap [mTemCap]); 11 received mTemCap, 27 did not. Rationale for mTemCap was good response (n = 7), good tolerance (n = 3) or pts' wishes (n = 1). Overall, 29 pts (48.3%) had stable disease and 14 pts (23.3%) achieved a partial response (PR); med reduction in responding pts was -56.7% (95%CI -76.4 to -33.3); 4 additional pts (6.67%) achieved a reduction >20% but <30%. Time to PR was 3.9 mo (95%CI 2.45-15.24); time to maximum response was 10.7 mo (7.2-11.8). By the end of follow-up, 95% and 75% of pts had stopped TemCap and progressed, respectively; estimated med PFS and overall survival (OS) were 10.1 mo (95%CI 6.7-14.2) and 27.3 mo (95%CI 16.35-NR), respectively. Achieving a PR was an independent factor (multivariable Cox regression) impacting on PFS (HR 0.2 (95%CI 0.1-0.6); p = 0.001); landmark analysis (excluding pts with early (3 mo) progression; n = 10) confirmed such findings.

Conclusions: Achieving a PR impacts on PFS in pts treated with TemCap. Although PR is an early event, maximum response is not achieved until later in pts' treatment/ follow-up; mTemCap until progression is appropriate for pts who are progression-free at 6 mo and have good tolerance to treatment.

Legal entity responsible for the study: N/A

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453P Efficacy of recombinant human endostatin combined with chemotherapy in advanced pancreatic neuroendocrine tumors

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Background: Dacarbazine or temozolomide, an oral analog of dacarbazine, showed activity against advanced pancreatic NETs when administered alone or in combination with other agents. Targeting pathways involved in angiogenesis, such as VEGFR TKI is also active in advanced pNETs. Endostatin is an endogenous angiogenesis inhibitor, rhEndostatin combined with chemotherapy prolonged overall survival compared with chemotherapy alone in advanced non-small cell lung cancer.

Methods: 14 patients with histologically confirmed, locally advanced or metastatic pancreatic well-differentiated NETs with radiologic progression within the previous 12 months received the study regimen: Temozolomide was administered orally 150-200 mg/m2/d, d1-7. Dacarbazine and 5-FU were both administered intravenously at a dose of 250mg/m2/d and 500mg/m2/d respectively, d1-5. rhEndostatin was administered intravenously at a dose of 15mg/d, d1-14, repeated every 21 days. CT/MRI was performed at baseline and every 3 cycles after initiation of treatment. Radiologic response was classified according to RECIST 1.1 criteria.

Results: Patients received a median of 6 treatment cycles (range, 2 to 8 cycles). Of the 14 patients, 6 patients received temozolomide and 8 received the DTIC + 5-FU combined with rhEndostatin. 5 patients used temozolomide as maintenance therapy, the median maintenance therapy cycles was 6 (range, 2 to 18 cycles). ORR was 43% (CR: 1 patient, PR: 5 patient), DCR was 86%, mPFS was 12 months, overall survival has not been reached. No grade 3/4 toxicity occurred.

Conclusions: rhEndostatin combined with temozolomide or darcarbazine-based chemotherapy was effective in treatment of advanced pNETs and was well tolerated.

Clinical trial identification: NCT01845675

Legal entity responsible for the study: Peking Union Medical College Hospital, Ethic Committee

Funding: None

Disclosure: All authors have declared no conflicts of interest.

454P Comparison of clinical efficacy of SST analogues therapy (lanreotide autogel vs. octreotide LAR) in treatment of patients with advance, non-resectable pancreatic neuroendocrine tumours (pNETs)

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Background: Use of somatostatin analogues can be considered in pancreatic NET G1/ G2 as a first-line therapy. This retrospective study aimed to compare the efficacy of octreotide long-acting release (OCT) and lanreotide Autogel (LAN) in patient with advanced G1/G2 pNETs, comparison between LAN and OCT in naïve patients, based on progression free survival (PFS).

Methods: Ninety-two patients with histological proven G1 or G2 pNETs were retrospectively analyzed (41 men; 51 women; mean age 53.7years [range 21-87 years]). The patients were assigned randomly to OCT (n = 42) and LAN (n = 50) groups. Evaluations included comparison of PFS between groups with LAN and OCT administered at 28-day intervals, objective response rate (ORR) calculated based on CT/MRI imaging performed every 6 month. The clinical efficacy was based on PFS and time to subsequent death/PD using Kaplan –Meier, radiological response was classified according to RECIST 1.0 criteria.

Results: Medain PFS for all patients was 16.0 months (CI 22.8-34.9); in LAN group PFS 22 months (CI 21.9-39.5) vs OCT 15 (CI 18.1-35,1), P = 0.28 (Cox Mantel test). The significant difference was noted in group of patients with G2 tumors LAN 22 months (CI 19.5-35.0) vs. OCT 7 months (CI 8.2-22.2) P = 0.01. Even higher significant difference was obtained in males group G2: LAN 23.5 (CI 16-44.6) vs. OCT 6.0 months (CI 3.3-14.3). There was no significant difference in female patients: LAN 17.5 mo (CI 15.4-34.8) vs. OCT 13 months (CI 8.2-29.4), but the trend favorable LAN over OCT. Additional analysis in patients with liver metastasis showed similar trend, but no significant difference. There was no difference in PFS between groups with G1 tumors in male or female patients and those without liver involvement.

Conclusions: Lanreotide Autogel is preferable SST therapy in G2 pNET, especially in male patients. Additional it seems to be also more effective in female patients but without statistical significance. The trend of better efficacy in terms of increase PFS seems to be in favor of LAN in patients with liver involvement as well. There was no significant difference in groups of patients with G1 pNEN and those without liver involvement.

Legal entity responsible for the study: Agnieszka Kolasinska-Cwikla

Funding: None

Disclosure: All authors have declared no conflicts of interest.

455P Metastatic neuroendocrine neoplasia (mNEN) treatments in over 70 years (y) old patients: A retrospective outcome analysis

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Background: NEN incidence increases with age. Elderly population is usually underestimated in clinical trials due to presence of co-morbidities and low performance status (PS) and thus prognosis' informations are lacking. Our study aims to analyze the outcome in a retrospective cohort of elderly metastatic NEN patients (pts) who underwent different treatments.

Methods: From June 2006 to march 2016 we collected data from pts ≥70 y with mNEN. Comorbidities were summarized by the Charlson Comorbidity Index (CCI). Kaplan-Meier method was used to estimate overall survival (OS), Cox's proportional hazard model to assess the impact of known prognostic factors. Adjusted hazard ratios (HR) were calculated with 95% confidence interval (95% CI).

Results: We identified 145 pts ≥70 y with mNEN. Pts characteristics were resumed in the table. Median follow up was 72.3 (53.2-85.1) months. First Line treatment was: somatostatin analog (SSA) in 79 pts, peptide radionuclide therapy (PRRT) in 23, chemotherapy (CHT) in 36 pts. Seven pts didn't receive first line treatment and 102 pts received more than 1 line treatment. PS ECOG and FDG PET results were identified as independent prognostic factors for OS assessed by a multivariate Cox regression model, with a higher risk for patients with PS ECOG ≥0 and with positive FDG PET, while age at diagnosis showed a hazard ratio of 1.10 (95%CI:0.99-1.26). Median OS was 5.1y (3.4-6.6). No difference in mOS were seen according to CCI. G1/G2 NEN pts who underwent PRRT as first line had a mOS of 6.5 y (3.3-NE), SSA 5.7 y (4.2-7) and CHT 5.9 y (0.4-NE) respectevely. G3NEN pts treated with CHT had a mOS of 1.5 y (1.0-2.5).

Table: 455P

Pts characteristics	N (%)
Male	86 (59.3)
Female	59 (40.7)
Age at diagnosis	
Median (range)	74 (70-87)
70-74 years	89 (61.4)
75-79 years	40 (27.6)
80+ years	16 (11.0)
PS ECOG	
0	59 (45.7)
1	60 (46.5)
≥2	10 (7.8)
Unknown(UK)	*16*
CCI	
0	57 (41.0)
1	52 (37.4)
2	19 (13.7)
≥3	11 (7.9)
UK	*6*
Syndromic	
Yes	42 (29.4)
No	101 (70.6)
UK	*2*
Grading	
G1	33 (26.2)
G2	62 (49.2)
G3	31 (24.6)
UK	*19*
Metastatic sites	
Hepatic	58 (40.0)
Extrahepatic	29 (20.0)
Both	58 (40.0)

Conclusions: Our results suggest a positive impact of various treatment on OS in mNEN elderly patients and the prognostic value of FDG PET and PS ECOG. Prospective clinical trial are needed to confirm our retrospective data.

Legal entity responsible for the study: Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (I.R.S.T.) IRCCS

Funding: None

Disclosure: All authors have declared no conflicts of interest.

456P Modified staging classification for gastric neuroendocrine carcinomas on the basis of the American Joint Committee on cancer

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Background: The purpose is to explore the value of the seventh edition of AJCC staging and improved AJCC staging in the evaluation of the prognosis of gastric neuroendocrine carcinoma (GNEC).

Methods: We analyzed retrospectively the clinical and pathological data of 427 GNEC patients from SEER database and 129 GNEC patients in single center. AIC and C index were used to evaluate the distinguishing capability of different TNM staging systems.

Results: In SEER database, the 5-year survival rate stratified by AJCC staging of GENC (I, IIa, IIb, IIIa, IIIb, IV) were 68%, 61%, 46%, 22%, 21%, and 10% respectively. While in single center, the 5-year survival rate of different stages were 100%, 60%, 27%, 16%, 22%, and 0% respectively. From the survival curve analysis, there are significant crossovers between the IIIB survival curves of SEER database as well as single center and those of IIIA and IIB. In SEER database, the T staging and the age of disease diagnosis were independent factors affecting the prognosis of IIIB patients. According to the T staging, the IIIB was divided into four subgroups: T1N1,T2N1, T3N1, and T4N1. According to the principle of similar survival rate, the new AJCC staging is composed of different stages: nI(T1N0M0), n IIa (T1N1M0, T2N0M0), n IIb (T2N1M0, T3N0M0), n IIIa (T3N1M0, T4N0M0), n IIIb (T3N1M0, T4N0M0) and n IV (T1-4NxM1). The survival curve of the new AJCC staging showed less crossover per stage, obtaining a smaller AIC value (1572 vs. 1583) and a smaller c-index (0.7505 vs. 0.7421). It is discovered that through employing the data of single center as external validation, the new AJCC staging can better distinguish different TNM staging.

Conclusions: Dividing IIIB of the seventh edition of AJCC staging into various substages has significant prognostic value and the new AJCC staging can better distinguish the stages of GNEC.

Legal entity responsible for the study: Changming Huang

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Disclosure: All authors have declared no conflicts of interest.

457P Predictive factors in GEP-NEN: The integrated role of Ki67, beta-catenin and morphology

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Background: The WHO 2010 classification divides gastro-entero-pancreatic neoplasms (GEP-NENs) into G1, G2 and G3, according to Ki67 and/or mitotic index. Several studies have proposed to further divide G3 diseases in at least two subgroups, defined by Ki67 and/or morphological features. We investigated the morphological or immunohistochemical features associated with poorer prognosis and weather the G3 category could be further divided according to such features.

Table: 457P Joint distribution of patients according to WHO 2010 classification by the results of the prognostic model

	New Prognostic model's macro groups by Ki67 grading								
WHO 2010 classification	m0,B01, Ki67 < =2	m0,B2 Ki67 < =2	m0,B01 2<Ki67 < =20	m0,B2 2<Ki67 < =20	m0,B01 Ki67>20	m0,B2 Ki67>20	m1,B01 Ki67 < =55	m1,B2 Ki67 < =55	m1 Ki67>55
G1 (Ki67 < =2)	89	0	0	0	0	0	0	0	0
G2(2<Ki67 < =20)	0	0	95	2	0	0	0	0	0
G3(20<Ki67 < =55)	0	0	0	0	17	7	12	9	0
G3 (Ki67 >55)	0	0	0	0	0	0	0	0	83

Methods: We evaluated 314 consecutive GEP-NEN patients. Surgical specimens of primitive tumors were assessed for morphology (m0: well-differentiated; m1: poorly-differentiated), Ki67 and beta-catenin (B01 absent or not-nuclear localization; B2 nuclear localization). Those features were correlated with overall survival (OS) and disease-free survival (DFS) after surgery by means of Cox multivariable models. The model performance was evaluated by means of Harrell's C index.

Results: Median follow-up was 84 months (95% CI: 74-103). Based on Ki67 only, the WHO 2010 classification allowed to distinguish three classes with different prognosis (5-year OS: ≤2%: 97.0%, 2-20%: 90.9%, >20%: 14.5%). When considering Ki67 as continuous variable, and by including also morphology and beta-catenin in the multivariable OS model, patient-specific estimates were obtained, thereby improving the prognostic classification, particularly for G3 patients, which could be split in further sub-groups (Table). Harrell's C index was 0.864. Similar results were obtained for DFS.

Conclusions: WHO 2010 classification stratifies the risk of OS and DFS for G1 and G2 diseases. On the other hand, the risk of death for G3 disease varies according to Ki67 values, morphology and beta-catenin. Morphology has the strongest predictive power, segregating two macro groups in which beta-catenin has a lower differential effect while a prognostic gradient by Ki67 (up to Ki67 ≤55) is evident.

Legal entity responsible for the study: FONDAZIONE IRCCS Istituto Nazionale Tumori, Milano Ethical Committee Approved 48/16

Funding: None

Disclosure: All authors have declared no conflicts of interest.

458P The preoperative blood lymphocyte-to-monocyte ratio acts as a superior prognostic factor and predicts tumor metastasis in gastric neuroendocrine neoplasms after surgery

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Background: The aim of this study is to investigate the prognostic significance of the preoperative blood lymphocyte-to-monocyte ratio (LMR) in gastric neuroendocrine neoplasms (g-NENs).

Methods: We enrolled 177 patients who had been diagnosed with g-NENs and undergone radical surgery. Receiver operating characteristic curve analysis was used to identify the optimal value for the LMR. Univariate and multivariate survival analyses were used to identify prognostic factors. A nomogram was adopted to predict recurrence free survival (RFS) and overall survival (OS) after surgery.

Results: The LMR was significantly lower in patients with g-NENs than in matched normal volunteers (NVs) ($P < 0.05$) and was associated with age, tumor site, tumor size, depth of invasion, the lymph node ratio (LNR) and lymphovascular invasion (all $P < 0.05$). Multivariate analysis demonstrated that the LMR was an independent prognostic factor for RFS and OS. The concordance index (C-index) of the nomograms for RFS (OS), which included the lymph node ratio, histological type and the LMR, was 0.776 (0.760), which was higher than the C-index of the traditional TNM staging system [0.678 (0.667)]. The recurrence rate was 38.9% (69/177), and the median time to recurrence was 10 months. We noted a significant correlation between the LMR and tumor recurrence, especially liver, peritoneal and lymph node metastases (all $P < 0.05$).

Conclusions: As an independent prognostic factor for survivals in patients with g-NENs, the LMR combined with the lymph node ratio and histological type had a more superior ability to predict clinical outcomes in post-surgery patients than the traditional TNM staging system. Patients with low LMRs require close surveillance to identify tumor recurrence early.

Legal entity responsible for the study: Changming Huang

Funding: None

Disclosure: All authors have declared no conflicts of interest.

459P Follow-up and recurrence in resected gastroenteropancreatic neuroendocrine tumours: A population-based study

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Background: Neuroendocrine tumours (NETs) are uncommon. Little data exist to guide follow-up in resected disease, with no consensus regarding the optimal follow-up frequency or modality. Follow-up imaging regimens are extrapolated from other gastrointestinal tumours. As NETs are heterogeneous, this may result in both over-use and underuse of investigations in patients.

Methods: A population-based retrospective cohort study using linked data from the Institute for Clinical Evaluative Sciences and the Ontario Cancer Registry (capturing more than 99% of incident cases in Ontario) was conducted to evaluate patients diagnosed with gastroenteropancreatic NETs in Ontario, Canada from 1994 to 2012. Recurrence-free survival and the frequency of cross sectional imaging (abdominal computed tomography (aCT), magnetic resonance imaging (aMRI) and ultrasound (aUS)) were the main outcomes.

Results: Nine hundred and thirty-six patients were identified with median follow-up 47 months. The mean age was 59, 51% were female, and distribution of primary cancers was: small intestine 47%, pancreas 20%, large intestine 21%, rectum 6.4%, stomach 6.0%. The median survival time to a composite outcome of recurrence or death was 7.2 years, and 9.5 years if censoring on death. The cumulative incidence of recurrence was 8.4% (95% CI 6.8% to 10.3%) within one year, 33.7% (95% CI 30.4% to 36.9%) within five years, and 48.5% (95% CI 44.4% to 52.4%) within 10 years. The rate of recurrence significantly increased with age (HR = 1.529 for age 50-70 compared to < 50, $p = 0.0003$) and pancreatic primary (HR = 1.463, $p = 0.0006$), but not income quintile ($p = 0.1071$), rurality ($p = 0.1931$) or gender ($p = 0.3787$). The rate of use of aCTs, aMRIs and aUS decreased over time, from 1.04 per 100 patient-days in months 1-3 to 0.22 at months 49-60. On average, 1.59 abdominal CTs per patient were performed in the first year, 0.83 in the second year and 0.52 in years 3-5.

Conclusions: Unlike colon cancer, significant numbers of NETs recur between 5-10 years after curative surgical resection. These data support the lengthening of follow-up for resected NETs to a minimum of 10 years. Future research should focus on the impact of imaging on early detection of recurrence and survival outcomes.

Legal entity responsible for the study: Sunnybrook Research Institute

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460P Elevated levels of 5-HIAA and CgA in patients with PanNETs from the CLARINET Study

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Background: While carcinoids frequently synthesize, and secrete serotonin into the circulation, and 5-HIAA is a common biomarker in the carcinoids, measurement of 5-HIAA in non-carcinoid PanNET patients (i.e. no hormone-related symptoms or non-functional) is not routinely recommended by international guidelines. The incidence of serotonin-producing PanNETs may be underestimated, with potential impact on clinical outcome when serotonin levels remain elevated. We sought to characterize 5-HIAA and CgA levels in PanNET patients who participated in the large placebo-controlled phase III CLARINET Study.

Methods: Evaluable data available for urinary 5-HIAA and serum CgA for patients with PanNET in CLARINET study were analyzed. Urinary 5-HIAA and Serum CgA were assessed at baseline and every 12 weeks thereafter through Week 96. Changes in urinary 5-HIAA and serum CgA levels were calculated using a non-parametric Wilcoxon 2-sample test. Biochemical response for urinary 5-HIAA or serum CgA was defined as baseline >upper limit of normal (ULN, 41.6 µmol/d 5-HIAA; 98.1 µg/L CgA) and ≥50% decrease from baseline or a decrease to a value ≤ULN on study.

Results: 91/204 patients in CLARINET had PanNETs. Evaluable data for urinary 5-HIAA and serum CgA concentrations were available in 79 and 88 patients, respectively. A substantial number of patients with PanNET had elevated (>ULN) urinary 5-HIAA levels (21/79; 27%) and/or serum CgA (63/88; 72%). Among the 21 PNET patients with baseline 5-HIAA >ULN, biochemical response was achieved in 85% (11/13) lanreotide-treated patients compared with 63% (5/8) in patients on placebo at the last available value ($p = 0.33$). Among patients with baseline CgA >ULN, biochemical response was achieved in 66% (19/29) of lanreotide vs. 18% (6/34) of placebo-treated patients ($p = 0.0002$). Limited sample sizes precluded robust analysis for statistically significant differences in the lanreotide vs. the placebo group among patients with elevated biomarkers at baseline and biochemical response.

Conclusions: The percentage of patients with elevated urinary 5-HIAA was unexpected. The concept of PanNET and secretion of serotonin may need to be redefined. The potential of 5-HIAA and CgA as biomarkers of response and follow-up in nonfunctioning PanNET is alluring, but requires further study. Data from additional prospective studies are needed to impact clinical practice guidelines.

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Legal entity responsible for the study: Ipsen Biopharmaceuticals

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461P The prognostic value of cytokeratin 7, 19, thyroid transcription factor-1 and CD117 expression in lung neuroendocrine tumors of various grades

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Background: Neuroendocrine tumors of the lung (NETL) are a wide range of tumors with various malignancy grades and prognosis.

Methods: We performed immunohistochemical assessment of the diagnostic biopsies and surgical specimens from 205 patients with NETL aged 55 ± 14 years and identified 61 (29,8%) typical carcinoids (TC), 44 (21,5%) atypical carcinoids (ATC), 84 (41%) small cell neuroendocrine carcinomas (SCNEC) and 16 (7,8%) large cell neuroendocrine carcinomas (LCNEC). Markers of neuroendocrine differentiation (synaptophysine, chromogranine A and CD56) and cytokeratins (CK) 7 and 19, thyroid transcription factor-1 (TTF-1), CD117 were used.

Results: Most often, the expression of CK7 and CK19 was found in LCNEC (71.4%, 10/14 and 91.7%, 11/12 respectively), less frequently, in ATC and SCNEC (52,8%, 19/36 and 52.4%, 22/42; 43,9%, 29/66 and 68,2%, 45/66 of cases, respectively), whereas in TC it was rare (13,3%, 6/45 and 19,3%, 11/57 respectively). The rates of CK7 and 19 expression were significantly lower in the TC, compared to the SCNEC and LCNEC ($p < 0.01$, χ.) The expression of TTF-1 was very rare in the TC (11,6%, 5/43 of cases) and significantly more often in ATC (60.5%, 23/38) and in SCNEC and LCNEC (79,2%, 57/72 and 75%, 9/12 of cases, respectively). TTF-1 expression was significantly less frequent in typical than in ATC, SCNEC and LCNEC ($p < 0.01$, χ.). The expression CD117 was absent in the TC (0%, 0/27), very rare in the ATC (17,4%, 4/23) and significantly more often in SCNEC and LCNEC (95,7%, 43/47 and 42,8%, 3/7 of cases, respectively).

Conclusions: Expression of TTF-1, CK7, 19 and CD117 in the NETL is characteristic for a less differentiated cell immunophenotype and allows for identification of the risk group with unfavorable clinical outcome among low-grade TC and ATC.

Legal entity responsible for the study: L. Gurevich

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461P An open-label, multicenter Phase 1b study of radium-223 + paclitaxel in cancer patients with bone metastases

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Background: Concomitant radium-223 (Ra-223) and chemotherapy is a possible option for cancer patients (pts) with bone metastases (mets). Both treatments impact hematologic parameters, and myelosuppression risk during coadministration is unknown. This phase 1b study (NCT02442063) in cancer pts with bone mets evaluated the safety of Ra-223 + paclitaxel (PTX) and the mode of interaction between treatments regarding myelosuppression.

Methods: Eligible pts had a confirmed malignant solid tumor with ≥ 2 bone mets and were candidates for PTX treatment. Treatment included 7 PTX cycles (90 mg/m^2 IV per wk as per local standard of care; 3 wk on/1wk off) combined with 6 Ra-223 cycles (55 kBq/kg IV; 1 injection every 4 wk, starting at PTX cycle 2). The primary end point was percentage of pts with neutropenia and thrombocytopenia during treatment with Ra-223 + PTX (cycles 2 and 3) vs PTX alone (cycle 1). A previously developed dose-exposure-response model describing the time course of PTX and Ra-223–induced suppression of absolute neutrophil counts was used to evaluate the mode of interaction (additive or synergistic) between Ra-223 and PTX.

Results: Of 22 enrolled pts, 15 were treated; 13 completed cycles 1-3 and were included in the pharmacodynamics analysis. Tumors in treated pts were breast (7 pts), prostate (4 pts), bladder (1 pt), non-small cell lung (1 pt), myxofibrosarcoma (1 pt), and neuroendocrine (1 pt). 7 pts had received ≥ 3 prior chemotherapy regimens. In the 13 pts who completed cycle 3, grade 3 neutropenia rates in cycles 2 and 3 were 31% and 8%, respectively, vs 23% in cycle 1; there were no cases of grade 4 neutropenia or grade 3/4 thrombocytopenia. No pts discontinued treatment due to toxicity from the treatment combination. Safety data for the breast cancer pt subset will be presented. The myelosuppression model showed an additive effect of Ra-223 to PTX-induced neutropenia, with an additional 10% average decrease in absolute neutrophil count vs PTX alone.

Conclusions: In pts with solid tumors and bone mets, Ra-223 was well tolerated when combined with PTX, with an additional 10% average decrease in neutrophil levels compared with PTX monotherapy. The combination should be explored further in pts with bone mets.

Clinical trial identification: NCT02442063

Legal entity responsible for the study: Bayer HealthCare Pharmaceuticals

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462P A nomogram based on tumor-associated neutrophil-to-lymphocyte ratio to predict survival prognosis for patients with gastric neuroendocrine neoplasms

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Background: This study investigated the predictive value of the tumor-associated neutrophil-to-lymphocyte ratio (TA-NLR) on clinical outcomes for patients with gastric neuroendocrine neoplasms (g-NENs) after radical surgery.

Methods: Data from 142 patients who were diagnosed with g-NENs and underwent radical gastrectomy at our department from March 2006 to March 2015 were prospectively collected and retrospectively analyzed. Receiver operating characteristic curve analysis was used to identify the optimal value for TA-NLR. Univariate and multivariate survival analysis were used to identify prognostic factors for g-NENs. A nomogram was adopted to predict RFS and OS after surgery.

Results: TA-NLR was not significantly associated with clinical characteristics (all $P > 0.05$). TA-NLR significantly correlated with tumor recurrence, especially with liver and lymph node metastasis (both $P < 0.05$). A multivariate Cox regression analysis identified the TA-NLR as an independent prognostic factor for recurrence-free survival (RFS) and overall survival (OS) (both $P < 0.05$). The concordance index (C-index) of the nomograms, including the TA-NLR, Ki-67 index and lymph node ratio, for RFS (OS) was 0.788(0.759) and was higher than the C-index of the traditional TNM staging system [0.672(0.663)].

Conclusions: TA-NLR was an independent prognostic factor for patients with g-NENs regarding RFS and OS. Nomograms with the TA-NLR, Ki-67 index and lymph node ratio had a superior ability to predict clinical outcomes for postoperative g-NENs patients, as well as the traditional TNM staging system.

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Disclosure: All authors have declared no conflicts of interest.

463P Plasma protein fingerprinting and machine learning for the diagnosis of small intestinal neuroendocrine tumors: The nordic NET biomarker group EXPLAIN study

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Background: Small intestinal neuroendocrine tumors (siNETs) are notoriously difficult to diagnose, especially in an early stage. The EXPLAIN study aimed to investigate

92 plasma proteins (PP), previously shown to be cancer related, in an attempt to improve the accuracy in diagnosis of siNETs.

Methods: This non-interventional exploratory study in the nordic countries analysed 136 patients with siNET from 17 hospitals and 144 age and sex matched controls (all with written consent). Exclusion criteria: NET not confirmed, previously treated for NET, other malignant diseases, chronic inflammatory disease, kidney or liver failure. Blood samples (4 ml) were obtained at first visit. Samples analysis used the Proseek Multiplex Oncology II assay (OLink) to measure relative levels of the 92-cancer related PP. In addition, chromogranin A (CgA) was analyzed centrally (Akademiska Lab. Uppsala). Data was subjected to statistical supervised learning techniques (SSLT): random forest and support vector machine.

Results: This is the first interim analysis. Patient characteristics: age 65±10 (mean±SD), 58% male, 48% G1 and 52% G2, 88% N1 and 65% M1, 23% >3 bowel mov/d and 11.5% >3 flushes/d. CgA (mean (SD), nmol/L) in 115 patients free from proton pump inhibitor treatment (PPI): 42.37 (86.62), in 21 NET patients with PPI: 68.41 (74.21), in 132 controls free from PPI: 3.67 (3.57) and in 12 controls treated with PPI: 11.83 (8.97). Several PP (>20) showed significant p<.005 different mean levels compared with controls (t-test with Satterthwaite correction). Ten valuable PP in the model: CgA, LYN, ABL1, DKN1A, TXLNA, MUC-16, EGF, MetAP 2, VIM and MK.

Table: 463P Comparison of SSLT models

	SVM – Radial	SVM – Linear	Random Forest
Accuracy (95% CI)	0.8429 (0.7362, 0.9189)	0.8714 (0.7699, 0.9395)	0.8857(0.7872, 0.9493)
Sensitivity	0.7647	0.7941	0.8824
Specificity	0.9167	0.9444	0.8889
AUC	0.9191	0.9428	0.9404

Conclusions: Both a high level of sensitivity and specificity (0.9) were obtained using our multi plasma protein strategy combined with SSLT for the diagnosis of siNET. Further development of the machine learning model is ongoing.

Legal entity responsible for the study: Peter Myrenfors Ipsen

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Disclosure: All authors have declared no conflicts of interest.

464P CXCR4 inhibition by ulocuplumab prevents EMT of pNET cells in vitro

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Background: NETs overexpress CXCR4. We have previously shown that stimulation of CXCR4 by its ligand SDF-1 promotes EMT and increases the distant tumor spread of NET cells. Ulocuplumab (Ulo) is a fully human IgG4 mAb designed to inhibit the binding of SDF-1 to CXCR4. We investigated the effects of Ulo in preventing pNET spreading *in vitro*.

Methods: Complement-dependent cytotoxicity (CDC), Ab-dependent cell cytotoxicity (ADCC), Ab-dependent cell phagocytosis (ADCP) and direct Ab-induced apoptosis were investigated using three pNET cell lines (BON1, CM, QGP1) treated with Ulo. Transcriptome profiling was performed by RNAseq following incubation with SDF-1 in the presence or absence of Ulo. Flow cytometry was used to characterize the EMT-related phenotype of NET cells, as well as their expression of immune checkpoints in response to EMT-inducing stimuli. Migration and invasion of pNET cells towards liver and bone fragments was evaluated by transwell assays. The effects of Ulo on the intracellular signaling activated by CXCR4 stimulation were investigated by western-blot (WB), while confocal microscopy assessed the nuclear expression of CXCR4 after high-quality nucleocytoplasmic fractionation.

Results: Ulo failed to induce CDC, ADCC and ADCP in pNET cell lines, in absence of significant direct tumor cell killing. Ligand stimulation of CXCR4 promoted an EMT-like transcriptional shift (upregulation of *SNAIL*, *ZEB1*, *SMAD2*), which was abrogated by Ulo. Treatment with SDF-1 induced cadherin switch, but was unable to alter the membrane expression of immune checkpoints including PD-L1, PD-L2 and CD38. Both *in vitro* migration and invasion of pNET cells towards liver and bone were significantly suppressed by CXCR4 blockade. Stimulation of CXCR4 induced the phosphorylation of Akt, ERK, and NF-kB, resulting in Vimentin overexpression as well as acquirement of mesenchymal patterns including enhanced spindle index. These effects, inhibited by Ulo, were paralleled by a substantial enrichment of CXCR4 on the nuclear membrane.

Conclusions: Ulo suppresses EMT in pNET cell lines by both disabling the intracellular signaling downstream CXCR4 activation and preventing its nuclear localization. The pathophysiology of nuclear CXCR4 needs to be investigated.

Legal entity responsible for the study: Department of Biomedical Sciences and Human Oncology, University of Bari, Bari, Italy

Funding: Department of Biomedical Sciences and Human Oncology, University of Bari, Bari, Italy

Disclosure: All authors have declared no conflicts of interest.

465P Interim baseline characteristics from RIFTOS MKI, a global non-interventional study assessing the use of multikinase inhibitors (MKIs) in the treatment of patients with asymptomatic radioactive iodine-refractory differentiated thyroid cancer (RAI-R DTC): A European subgroup analysis

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Background: RIFTOS MKI was designed to compare the time to symptomatic progression from study entry in patients with RAI-R DTC for whom there was a decision to treat or not to treat with an MKI in the real-life setting. Here, we report interim baseline characteristics for a subgroup of patients from Europe.

Methods: RIFTOS MKI is a non-interventional study enrolling patients from USA, Japan, Europe, and rest of the world with asymptomatic RAI-R DTC. The decision to initiate MKIs at study entry was at the discretion of the treating physician. Final analysis will be performed once 700 patients have been enrolled and the last enrolled patient has been followed for 24 months.

Results: Of the 80 patients enrolled from Europe, the median duration of observation was 165 days; 51% were male and the median age was 67 years. Most patients had an ECOG performance status of 0 or 1 (96%) and distant metastasis at initial visit (81%). The most frequent histology was papillary (61%). The median time from initial diagnosis of DTC to study entry was 7.7 years. RAI refractoriness was mainly due to lack of RAI uptake (70%) and the median time from RAI classification to initial visit was 25 months. The average dose per RAI treatment and median cumulative activity of RAI were 4.6 and 13.0 GBq, respectively.

Conclusions: The interim baseline characteristics results presented here are similar to those previously reported in phase III studies. The study is ongoing.

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Legal entity responsible for the study: Bayer

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466P Mixed adeno-neuroendocrine carcinoma (MANEC) of the gastroenteropancreatic (GEP) tract: A multicentre retrospective study

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Background: MANEC is a rare entity and evidence on its prognosis and management is limited.

Methods: Demographic/clinicopathological/survival data of consecutive patients (pts) with a diagnosis of MANEC (2010 WHO criteria) from 4 European centres were retrospectively reviewed.

Results: Fifty-three pts were identified (01/06-03/17); median (med) age: 62 yrs (range 34-89), male: 70%, ECOG PS 0-1: 60%, with primary tumours from small/large bowel in 34 (64%), oesophagus/stomach: 13 (24.5%), pancreas/biliary tract: 5 (9.5%), unknown (UNK): 1 (2%). Forty percent had an adult comorbidity evaluation (ACE)-27 score of 0. The neuroendocrine (NE) component (predominant histology in 40%) was poorly-differentiated (PD) in 45 (85%) [Ki-67≥55%: 58%]. Most frequently-expressed immunohistochemical (IHC) markers were synaptophysin (100%), chromogranin A (CgA) (58.5%) and CDX2 (51%). Histology was PD NE in 64% from recurrent/metastatic sites (n = 14 pts). Of 28 (53%) pts with localised disease (LA), 26 (93%) had curative surgery (7 had neoadjuvant chemo-radiotherapy (CT-RT), 6 adjuvant CT, 1 peri-operative CT), 1 (3.5%) had definitive CT-RT and 1 (3.5%) had UNK management; 16 (57%) recurred. Forty-one pts (77%) were treated for advanced (adv) disease: 20 (49%) platinum-based CT, 3 (7%) irinotecan-based CT, 1 (2.4%) gemcitabine, 3 (7%) UNK CT regimen, 1 (2.4%) RT, 1 (2.4%) CT-RT, 11 (27%) best supportive care (BSC), and 1 (2.4%) UNK management. Med follow-up time was 10.4 months (mo) (95% Confidence Interval (CI) 5.15-13.09). Med overall survival (OS) for all pts was 18.6 mo (95% CI 11.4-40). Med recurrence-free survival and OS in pts with LA was 19.4 mo (95%CI 5.8-30.9) and 21 mo (95%CI 12.1-40). Med progression free survival (PFS) and OS in pts with adv disease was 4.6 mo (95%CI 3.3-6.7) and 13.6 mo (95%CI 8.8-33.1). On univariable analysis, ACE-27 score (0 vs ≥ 1) was prognostic for better PFS and OS (both $p < 0.05$); IHC negativity for CgA and active treatment (vs BSC) were prognostic for better PFS (both $p < 0.05$).

Conclusions: PD NE histology in MANECs was predominant in both diagnostic and recurrent/metastatic tumour samples. Active treatments were offered to most pts but more effective therapy is clearly needed.

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Funding: The Christie

Disclosure: All authors have declared no conflicts of interest.

467P Incidence of adrenal gland tumor as a second primary malignancy: SEER based database

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Background: Adrenal gland tumors are sporadic and heterogeneous, with an incidence (excluding childhood neuroblastoma) of 0.05% in the US. Advances in cancer treatment in the last few decades have resulted in increased survival in most paediatric and adult cancer types. The aim here is to report the incidence of adrenal gland tumors as a second primary tumor based on data from the SEER database.

Methods: Data from the Surveillance, Epidemiology, and End Results 'SEER' program of the National Cancer Institute, using the SEER*stat software (version 8.3.2) was obtained. All cancer sites using the Multiple Primary Standardized Incidence Ratios 'MP-SIR' session were selected. SEER 13 Regs Research Data from1992 to 2013 was used.

Results: Data from a total of 2,887,468 persons with cancer were reviewed, 117 of whom had suffered second primary adrenal tumors. One of these patients had two events of adrenal cancer as a second primary, resulting in a total of 118 incidences. The overall standardized incidence ratio (SIR) of adrenal gland tumor as a second primary was 1.49. A high percentage of this event was found in elderly patients, especially those of white race. High incidence of the event was detected in specific primary tumor sites: hypopharynx (O/E=44.59), stomach (O/E=4.95), small intestine (O/E=8.86), liver (O/E=8.74), breast (O/E=1.78), kidney and renal pelvis (O/E=3.19), other endocrine including thymus (O/E=38.27), nodal NHL (O/E=3.79), and Chronic Myeloid Leukemia (O/E=11.15).

Conclusions: Little is available in the literature about adrenal gland tumors as a second primary tumor. Its incidence is high in both white race and elderly cancer survivors in the US. The risk of cancer survivors suffering from a second primary adrenal gland tumor should receive more attention in the US. This would ideally be through follow-up programs at specialized national cancer networks, especially for rare tumors like those of the adrenal gland.

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468P Activity of temozolomide (TMZ) in patients (PTS) with malignant pheochromocytoma or paraganglioma (MPP): A mono-institutional retrospective study

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Background: MPP are very rare neuroendocrine tumors and, currently, there is no standard chemotherapy for their treatment. TMZ showed some benefit in digestive neuroendocrine tumors. We investigate TMZ activity in PTS with MPP.

Methods: Retrospectively, we evaluated TMZ activity in MPP PTS treated at our oncological center, Veneto Institute of Oncology, from January 2015 to March 2017. The inclusion criteria were: pathological diagnosis of MPP, ECOG PS 0-2, no haemopoietic, renal and hepatic abnormalities. TMZ schedule was 150-200mg/m^2 for 5 consecutive days every 28 days until progression disease or unacceptable toxicity. CT scan and urinary concentrations of metanephrines were performed every 12 wks; evaluation of tumor response was performed according to RECIST 1.1 criteria. Germinal mutational analysis of the genes of susceptibility to pheochromocytoma/paraganglioma (SDHx, MAX, TMEM127, RET, VHL, FH) was performed. Aberrant hypermethylation of MGMT promoter was analyzed on DNA obtained from surgical tissue. Median OS and PFS were estimated by the Kaplan-Meier method. Toxicity was evaluated by CTCAE v.4.

Results: We enrolled 12 consecutive PTS; 7 were males; ECOG PS was 1 and 2 in 9 and 3 PTS. MAX gene was mutated in 1 PT. SDHB gene was mutated in 2 PTS. MGMT promoter was methylated in 1 patient. No other genetic mutations were found. 5 PTS were already treated with a prior chemotherapy (3 sunitinib, 1 capecitabine, 1 dacarbazine) and 4 with a prior MIBG. 9 PTS were evaluable for response: 2 PTS had a partial response, 5 stable disease, 2 progressive disease. Median follow up was 9.2ms (range 1.1-28ms). 2 PTS received TMZ for more than 2 years and other 2 PTS for more than 1 year. Median PFS and OS were not reached (95% CI = 3.4ms-n.a.; 6.2ms-n. a, respectively). Urinary metanephrines levels seem to correlate with response. Hypertension descreased significantly in 5 PTS during TMZ treatment. No grade 3-4 toxicity was recorded.

Conclusions: TMZ is an active and safe treatment for MPP, regardless of previous treatment. A prospective phase II study is ongoing.

Legal entity responsible for the study: Giuseppe Lombardi

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Disclosure: All authors have declared no conflicts of interest.

469P Neuroendocrine carcinoma of the uterine cervix: A retrospective monocentric study

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Background: Neuroendocrine cervical carcinoma (NECC) is a very aggressive and rare disease. To date, only 2 prospective studies with scarce patient numbers have been reported in the literature. Here we studied a NECC patients (pts) cohort treated with current anticancer treatment modalities.

Methods: All pts with NECC were retrieved from 1996 to 2013 in our institute (n = 14). 3D-conformal radiation therapy combined to concomitant chemotherapy (RT-CT) was performed to all pts. Chemo- regimen (CT) was cisplatin plus etoposide or carboplatin plus etoposide. Mean total dose to clinical target volume (CTV) was 48 Gy.

Results: Pts and treatments characteristics. Mean age was 48.5 years old. Most of pts had a loco regional disease (n = 11): stage IA (n = 1), IB (n = 1), IIA (n = 2) and IIB (n = 7); 3 pts were stage IVB. Pelvic and/or lombo-aortic lymph nodes involvement was observed in 42.8% pts (n = 6). Among them, 3 pts were treated with an extended lombo-aortic radiation field. Among the entire cohort, 2 treatment modalities were distinguished: (i) most of pts were treated with neoadjuvant CT followed by concurrent RT-CT (n = 9). Either pulsed-dose rate (PDR) brachytherapy (n = 4) or colpo-hysterectomy (=3) was performed according to tumor response. Adjuvant CT was performed to 3 pts in this subgroup (mean number of cycle: 3); (ii) colpo-hysterectomy followed by concomitant RT-CT and PDR brachytherapy (n = 1), adjuvant CT delivered to 1 patient (3 cycles). Pts outcome. Median follow up was 10 years (range,

0.3-11.2). Median overall survival (OS) was 1.9 years; (IC95% [0.8 –NC]); 1-, 2- and 5-y OS were 79%, 48% and 40% respectively. Median progression free survival (PFS) was 11.7 months (IC95% [6 - 59]); 1-, 2- and 5- y PFS were 50%, 29% and 21% respectively. At the time of study analysis, 5 pts were still alive without any progression disease and are considered as long patient survivor (follow up at least more than 6 years).

Conclusions: Despite the small number of pts in our study, pts outcome was consistent with the literature. This study showed a large variety of treatment modalities. To date, there is no consensus on how to treat these pts. However, owing to poor pts outcome, aggressive treatment modalities are probably required.

Legal entity responsible for the study: Christine Kerr

Funding: None

Disclosure: All authors have declared no conflicts of interest.

470TiP AGITG NABNEC: A randomised phase II study of nab-paclitaxel in combination with carboplatin as first line treatment of gastrointestinal neuroendocrine carcinomas

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Background: Neuroendocrine carcinomas (NEC WHO grade 3) are aggressive cancers that are rapidly fatal. There have been no randomised trials to date to establish standard therapy for advanced gastrointestinal (GI) NECs. Etoposide and carboplatin are used by extrapolation from small cell lung cancer data. Paclitaxel is also active in NECs but there is no data on the role of nab-paclitaxel. This randomised study aims to establish if carboplatin and nab-paclitaxel combination is an effective and tolerable treatment for advanced GI NECs.

Trial design: NABNEC has commenced as a randomised phase II multicentre trial enrolling adults with advanced and/or metastatic non-resectable GI NECs. Patients are randomised to: Arm A (n = 47) IV nab-paclitaxel 100 mg/m^2 on Day 1 every week and IV carboplatin AUC = 5 on Day 1 every 3 weeks OR: Arm B (n = 23) IV etoposide 100mg/m^{2}on Days 1-3 every 3 weeks and IV carboplatin AUC = 5 on Day 1 every 3 weeks. Treatment will continue until disease progression or unmanageable toxicity. The primary endpoint is objective response rate (RR) by RECIST 1.1. At 6 months, the RR in the intervention group would need to be at least 50% to justify further investigation. A total sample size of 70 patients with a 2:1 randomisation (intervention to control) will have 80% power with 95% confidence to rule out a 30% objective RR in favour of a more clinically relevant RR of 50% at 6 months. Secondary endpoints include progression free survival, overall survival, safety as measured by NCI-CTCAE V4.03, and quality of life using EORTC QLQC30 and QLQ-GINET21 questionnaires. Translational research endpoints include (1) blood and tissue biomarkers (prognostic and/or predictive) correlated with clinical endpoints including (a) circulating tumour cells, (b) mutation profile by whole exome sequencing, (c) DNA methylation profile and (2) utility of 18-fluoro-deoxyglucose positron emission tomography (FDG-PET) imaging as an early predictor of response and association of SUV max with clinical endpoints. NABNEC has opened to recruitment at 9 study sites and is currently enrolling patients. The randomised NABNEC study will run at 20 sites in Australia and New Zealand. ANZCTR # 12616000958482.

Clinical trial identification: AG0215NET/CTC0137 Version 1.1 29 February 2016

Legal entity responsible for the study: Australasian Gastro-Intestinal Trials Group

Funding: National Health and Medical Research Council (NHMRC); Specialised Therapeutics Australia PTY Ltd (STA)

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471TiP A multicentre, randomised, double-blind, parallel-group, placebo-controlled trial of apatinib in local progressive or metastatic radioactive iodine-refractory differentiated thyroid cancer

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Background: Radioactive iodine-refractory differentiated thyroid cancer (RAIR-DTC) is a big challenge in the management of thyroid cancer. Sorafenib and lenvatinib are the 2 FDA-approved tyrosine kinase inhibitors (TKIs), which might not be affordable for most of the Chinese patients (pts). Apatinib is an oral TKI targeting VEGFR-2, with a patient assistance program available in China. It achieved a quick Tg decline of 21% 2 weeks later and an objective response rate (ORR) of 90%, showing promising efficacy in RAIR-DTC (Lin et al, ATA 2016, Short Call Poster 65; Lin et al, Oncotarget, Epub Feb. 02, 2017). Thus, this study aimed to further evaluate the efficacy and safety of apatinib in treating RAIR-DTC.

Trial design: This study is a multicentre, randomised, double-blind, parallel-group, placebo-controlled, phase III trial in China. Adult pts with locally advanced or metastatic RAIR-DTC are eligible. The inclusion criteria include at least one measurable lesion; disease progression within the past 12 months; and ECOG PS 0–2. Pts are defined as RAIR-DTC if they have target lesion(s) without iodine uptake, received one RAI treatment (≥3.7 GBq [≥100 mCi]) but progressed within the past 12 months, received two RAI treatments or more with a time interval of less than 12 months and progressed at least 12 months later), or received cumulative RAI activity over 22.2 GBq (≥600 mCi). Previous targeted therapy is not allowed. Enrolled patients will be randomly assigned to receive apatinib (500 mg qd) and placebo, respectively. Four weeks is defined as one cycle. Dose increase to 750 mg and dose reduction to 250 mg are allowed. The primary endpoint is progression free survival. The secondary endpoints include disease control rate, ORR, duration of response, changes in serum Tg and TgAb concentration, quality of life, and safety. A multiple Cox proportional hazards model is used to evaluate the hazard ratios after adjusting iodine uptake, metastatic lesion site, gender, and age. 118 pts will be recruited assuming a 106.9% increase in median PFS in the apatinib arm compared with the placebo arm. As of 2nd May 2017, 3 eligible patients have been enrolled.

Clinical trial identification: NCT03048877 (Release date: February 7, 2017)

Legal entity responsible for the study: Yansong Lin

Funding: None

Disclosure: All authors have declared no conflicts of interest.

472TiP Phase 2 clinical investigation of BPM31510 (ubidecarenone) alone and in combination with gemcitabine in patients with advanced pancreatic cancer

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Background: BPM31510 is an ubidecarenone lipid nanodispersion that switches cancer energy generation from glycolysis to mitochondrial oxidative phosphorylation to elicit anticancer effect. BPM31510 is well tolerated as a monotherapy and at an established MTD of 110mg/kg in combination with Gemcitabine in a Phase I clinical trial. Preclinical *in vivo* pancreatic models demonstrate that BPM31510 alone and in combination with gemcitabine significantly improves duration of survival; supporting the Phase 2 evaluation of BPM31510 in patients with advanced metastatic adenocarcinoma.

Trial design: Eligible patients (aged ≥ 18 y) relapsed/refractory to standard treatment (ST) and met inclusion/exclusion criteria. Each patient receives 110mg/kg IV BPM31510 in a 144-hour infusion alone or in combination with gemcitabine. Tumor response is evaluated at wk10 and then every 8 wks. Investigator observations and reports by treated patients provide clinical assessments not specifically defined in the protocol. This study initially will enroll ten (10) patients in the BPM31510 (monotherapy arm) and ten (10) patients in the BPM31510 plus gemcitabine (combination therapy arm) with intent to enroll the additional 15 patients into the applicable treatment arm(s) into the expansion stage based on RECIST v1.1 clinical response. The goal is to evaluate the Overall Response Rate (ORR) in patients treated with BPM31510 alone or in combination with gemcitabine along with Overall Survival (OS); Progression-Free Survival (PFS); Time to Progression (TTP); Tumor Response using Adaptive Molecular Responses (multi-omic molecular profiling); Evaluate Change in CA 19-9 levels and patient reported Quality of Life using the validated FACT-HEP patient-reported outcomes instrument.

Clinical trial identification: BPM31510IV-05

Legal entity responsible for the study: BERG, LLC

Funding: BERG, LLC

Disclosure: A. Niewiarowska: Clinical investigator paid by BERG, LLC to conduct studies. R. Sarangarajan: Employee, co-founder and has stock options of BERG, LLC. D. Lucius: Employee and has stock options of BERG, LLC. N. Narain: Employee, co-founder and has stock options of BERG, LLC R.K. Raminathan: Clinical investigator paid by BERG, LLC to conduct studies. M. Hidalgo: Clinical investigator paid by BERG, LLC to conduct studies.

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GASTROINTESTINAL TUMOURS, COLORECTAL

4730 Three versus six months' adjuvant oxaliplatin-based chemotherapy for patients with stage III colon cancer: Per-protocol, subgroups and long-lasting neuropathy results

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Background: The International Duration Evaluation of Adjuvant chemotherapy (IDEA) collaboration was established to combine data from 6 randomized trials to assess whether 3-month (3M) of oxaliplatin/fluoropyrimidines-based adjuvant chemotherapy is non-inferior to 6-month (6M) for 3-year disease-free survival (DFS) in stage III colon cancer (CC).

Methods: IDEA France randomized patients (pts) between 3M and 6M of chemotherapy with mFOLFOX6 or XELOX (physician choice). DFS was estimated using the Kaplan–Meier method and described using a 3-year DFS rate with 95% confidence interval (CI). Cox-proportional-hazard models were performed to estimate the hazard ratios (HRs) and 95% CIs. We present here the results in the modified ITT (mITT: pts receiving at least one dose of treatment) and modified per-protocol (mPP: pts receiving 3M in the 3M arm and >5M in the 6M arm) populations. Subgroups and long lasting neuropathy results are also reported here.

Results: From May 2009 to May 2014, 2022 pts were randomized from 129 centers and 2010 (99%) and 1757 (87%) were included in the mITT and mPP populations, respectively. With a median follow-up of 4.3 years, the 3-year DFS rate was 72% and 76% (HR = 1.24; 95% CI 1.05–1.46, p = 0.01) for the 3M and 6M mITT populations, respectively and 72% and 78% (HR = 1.36; 95% CI 1.14–1.63, p = 0.0008) for the 3M and 6 M mPP populations. In the mITT FOLFOX treated population (90% of pts), 3-year DFS was 81% (3M) and 83% (6M) for T1-3/N1 pts (N = 1106, HR = 1.15 95%CI 0.89-1.49) and 58% (3M) and 66% (6M) for T4/N2 pts (N = 702, HR = 1.44 95%CI 1.14-1.82). Grade >1 neuropathy was observed in 36% and 67% of pts (p < 0.0001) in the 3M and 6M arms, respectively. With a median follow-up of 3.6 years, final residual grade >1 neuropathy was 2.8% and 7.4% (p < 0.0001), in the 3M and 6M arms, respectively.

Conclusions: The IDEA France study, with 90% of pts treated with mFOLFOX6, shows that 6M adjuvant treatment is superior to 3M. However, this difference was not significant in the mITT and mPP T1-3N1 populations suggesting that 3M of the mFOLFOX6 regimen could be an option for these pts. Clinically relevant (grade>1) neuropathy was significantly higher in the 6M arm, with long-lasting neuropathy in 7.4% of pts.

Clinical trial identification: Registration Number (European Union Drug Regulating Authorities Clinical Trials): 2009-010384-16

Legal entity responsible for the study: GERCOR - Groupe Coopérateur Multidisciplinaire en Oncologie

Funding: French Ministry of Health and French National Cancer Institute (INCa)

Disclosure: J. Taieb: Advisory board or Board of directors: Sanofi, Baxalta, Roche, Merck, Amgen, Lilly, Celgene. F. Bonnetain: Advisory board or Board of directors: Roche, Ipsen, Amgen, Nestle, Novartis; corporate-sponsored research: Novartis, Roche. L. Mineur: Advisory board or Board of directors: Amgen, Sanofi, Bayer, Roche; corporate-sponsored research: Sanofi, Merck, Chugai. J. Bennouna: Advisory board or Board of directors and honorarium: BMS, Roche, Boehringer Ingelheim, AstraZeneca. D. Vernerey: Honorarium: Janssen, Celgene. Advisory board: HallioDx. C. Lepere: Advisory board or Board of directors: Ipsen. O. Bouche: Advisory board or Board of directors: Merck Serono, Roche, Amgen. M. Ychou: Advisory board or Board of directors: Roche, Bayer, Amgen, Lilly. T. André: Advisory board or Board of directors: BMS, Amgen, Roche; corporate-sponsored research: BMS, Roche; honoraria: Baxter, Bayer, Lilly, MSD, Sanofi, Mundipharma, Novartis. All other authors have declared no conflicts of interest.

4740 Treatment outcome according to tumor RAS mutation status in TRICOLORE trial: A randomized phase 3 trial of S-1 and irinotecan plus bevacizumab versus mFOLFOX6 or CapeOX plus bevacizumab as first-line treatment for metastatic colorectal cancer

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Background: Combination therapy with oral fluoropyrimidine and irinotecan (CPT-11) has not yet been established as first-line treatment for metastatic colorectal cancer (mCRC). However, several studies of S-1 and CPT-11 plus bevacizumab (Bmab) combination therapy have shown promising efficacy in mCRC, suggesting the potential to replace mFOLFOX6 or CapeOX plus Bmab. We performed a randomized phase 3 trial to determine whether S-1 and CPT-11 plus Bmab is non-inferior or superior to mFOLFOX6 or CapeOX plus Bmab in terms of progression-free survival (PFS).

Methods: The TRICOLORE trial was a randomized, open-label, phase 3 trial. Chemotherapy-naïve patients with mCRC were randomized to receive either mFOLFOX6 or CapeOX plus Bmab (group A) or S-1 and CPT-11 plus Bmab (group B; 3-week regimen: 7.5 mg/kg Bmab, 150 mg/m^2 CPT-11 on day 1, and 40 − 60 mg S-1 twice daily for 2 weeks, followed by a 1-week rest; or 4-week regimen: 5 mg/kg Bmab, 100 mg/m^2 CPT-11 on days 1 and 15, and 40 − 60 mg S-1 twice daily for 2 weeks, followed by a 2-week rest). The primary endpoint was PFS. The non-inferiority margin was a hazard ratio (HR) of 1.25 based on the assumption of a median PFS of 11/12 months in group A/group B (power 0.85, 1-sided alpha 0.025). The primary tumor RAS status of patients consented to submit tissue sample were centrally analyzed.

Results: A total of 487 patients were enrolled from June 2012 to September 2014. Data were analyzed after confirming >374 events as planned. All demographic factors were well balanced. Median PFS was 10.8 months in group A and 14.0 months in group B (HR 0.85, 95% CI: 0.70–1.03, p < 0.001 for non-inferiority, p = 0.087 for superiority). The RAS mutation status was evaluable in 67.6%. In the RAS wild-type subgroup, median PFS was 11.6 months in group A and 15.9 months in group B. In the RAS mutant-type subgroup, median PFS was 9.3 months in group A and 11.3 months in group B.

Conclusions: S-1 and CPT-11 plus Bmab was non-inferior to mFOLFOX6 or CapeOX plus Bmab with respect to PFS and has now become a recommended 1st-line treatment for mCRC irrespective of RAS status.

Clinical trial identification: UMIN000007834 2012/05/11

Legal entity responsible for the study: The Tokyo Cooprative Oncology Group

Funding: The Tokyo Cooprative Oncology Group (with funding from Taiho)

Disclosure: Y. Komatsu: Other substantive relationships: Taiho Pharmaceutical, Lilly, MSD, Ono Pharmaceutical, Novartis, Chugai Pharma, Yakult, Merck Serono, Pfizer, Bayer. A. Takashima: Corporate-sponsored research: Taiho Pharmaceutical, Gilead Sciences, Merck Serono. M. Gamoh: Corporate-sponsored research: Taiho Pharmaceutical, Gilead Sciences, Merck Serono. H. Shimodaira: Corporate-sponsored research: Taiho, Eisai, Bayer. H. Baba: Advisory board or Board of directors: Taiho Pharmaceutical Co., Ltd.; corporate-sponsored research: Taiho Pharmaceutical Co., Ltd. C. Ishioka: Mochida, Kyowa-K, Eisai, Chugai, Tsumura, Novartis, Merck Serono, Daiichi Sankyo, Takeda, Nihon-Kayaku, Yakult, Taiho, Ono, Astellas, Asahi Kasei, Kissei, Bristol-Myers Squibb, Mochida, Chugai, Novartis, Lilly, Bayer. A. Sato: 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: Speakers' bureau: Chugai Pharmaceutical, Eli Lilly Japan, Bayer Yakuhin, Takeda Pharmaceutical, Taiho Pharmaceutical, Merck Serono. S. Morita: Corporate-sponsored research: Taiho; honorarium: Taiho. All other authors have declared no conflicts of interest.

475O mFOLFOXIRI + panitumumab versus FOLFOXIRI as first-line treatment in patients with RAS wild-type metastatic colorectal cancer m(CRC): A randomized phase II VOLFI trial of the AIO (AIO-KRK0109)

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Background: Triple chemotherapy with an anti-EGFR reported promising activity with some safety concerns in single arm phase II trials. The randomized VOLFI trial evaluated activity and safety of mFOLFOXIRI + panitumumab versus FOLFOXIRI in ECOG 0-1, primarily non-resectable mCRC patients.

Methods: Prospective 2:1 randomized, multi-center, phase II trial comparing mFOLFOXIRI (Oxaliplatin 85 mg/m2, Irinotecan 150 mg/m2, 5-FU 3000mg/m2 cont. 48h, LV 200 mg/m2) + Panitumumab 6 mg/KG (arm A) with FOLFOXIRI (Ox 85 mg/m2, Iri 165 mg/m2, 5-FU 3200mg/m2 cont. 48h, LV 200 mg/m2; arm B), both arms q2w. Cohort 1: irresectable mCRC; cohort 2: chance of secondary resection of metastatic lesions. Primary endpoint was ORR, secondary endpoints were secondary resection rate (cohort 2), DCR, PFS, OS, toxicity, quality of life. Financially supported by an unrestricted grant from Amgen.

Results: A total of 96 patients were randomized (63 arm A, 33 arm B). In arm A and B 20 (31.7%) and 11 (33.3%) patients belonged to cohort 2, respectively. ORR was 85.7% in arm A and 54.5% in arm B ($p = 0.0013$, OR 5.000; 95%-CI 1.870-13.370). DCR was 96.8% in arm A and 78.8% in arm B ($p = 0.0071$, OR 8.212). In arm A and B 53 (84,1%) and 25 (75.8%) tumors were left sided, 10 (15.9%) and 6 (18.2%) were located in the right colon, respectively. ORR in Arm A was 90.6% versus 60.0% ($p = 0.0288$, OR 6.400) and in Arm B 60.0% versus 50% (p=n.s.) for left and right located CRC, respectively. ORR between arms A and B comparing left and right sided CRC was 90.6% versus 60.0% ($p = 0.0039$, OR 6.400; 95%-CI 1.889-21.679) and 60.0% versus 50.0% (p= n.s.), respectively. Secondary resections in cohort 2 were 60% ($n = 12$) and 36.4% ($n = 4$) in arms A and B, respectively. Serious adverse advents grade 3-5 occured in 45.3% and 24.2% in arms A and B, respectively ($p = 0.0496$).

Conclusions: mFOLFOXIRI plus panitumumab results in significantly higher response rates compared to FOLFOXIRI in RAS wild-type mCRC. Response rates, however, are differential according to tumor sidedness. High secondary resection rates were observed. Toxicity is manageable in younger fit patients with ECOG 0-1. PFS, OS, QL and TR data are still immature and will be presented at the meeting.

Clinical trial identification: NCT01328171

Legal entity responsible for the study: AIO

Funding: Amgen

Disclosure: M. Geissler: Honoraria and advisory board from Amgen All other authors have declared no conflicts of interest.

476O Neoadjuvant FOLFOX 4 versus FOLFOX 4 plus cetuximab versus immediate surgery for high-risk stage II and III colon cancers: A phase II multicentre randomised controlled trial (PRODIGE 22)

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Background: Neoadjuvant chemotherapy has proven valuable in several tumors, but not in colon cancer (CC). The present randomized phase II trial addressed this issue in patients (pts) with locally advanced CC.

Methods: Pts with resectable CC deemed as high risk T3 (extramural tumor invasion > 5 mm), T4 and/or N2 (3 or more visible lymph nodes or 1 node >10mm diameter) on initial abdominopelvic CT-scan were randomized to either receive 6 months of adjuvant FOLFOX after colectomy (arm A control), or neoadjuvant FOLFOX for 4 cycles before surgery and 8 cycles after (arm B). In RAS wild-type pts a third arm testing perioperative FOLFOX + cetuximab has been added prior to colectomy (arm C). The primary endpoint of the study was the rate of major pathological Tumor Regression Grade (TRG) as defined by Ryan centrally assessed by 2 pathologists blinded to the pts treatment. The secondary endpoints included toxicity, perioperative morbidity, carcinologic quality and completeness of the surgery. Analysis was by intention to treat.

Results: 120 pts from 37 French centres were enrolled, 94% completed preoperative chemotherapy. All but 5 pts (disease progression $n = 2$, metastatic disease at inclusion $n = 1$, non resectable tumor $n = 1$, death $n = 1$) in the preoperative arms were resected. 95% and 98% of patients underwent R0 resection in the preoperative arms and control arm, respectively. No significant differences in severe postoperative morbidity rates (Dindo Grade >3) were seen between arm A (13.7%), B (8.2%) and C (14.3%) ($p = 0.64$). Major pathological responses (TRG 1-2) were observed in 7.7%, 44.2%, and 6.3% in arm A, B and C respectively ($p < 0.001$).

Conclusions: Preoperative FOLFOX for locally advanced resectable CC is feasible with acceptable toxicity/morbidity and high TRG. A phase III trial to establish whether these encouraging results translate into improved long-term oncological outcome is now warranted.

Clinical trial identification: NCT01675999

Legal entity responsible for the study: AP-HP

Funding: Merck, PHRC 2010

Disclosure: O. Bouche: Roche, Merck-Serono, Amgen, Lilly, Boehringer Ingelheim, Bayer J-F. Seitz: Merck, Sanofi. J. Taieb: Abbvie, Amgen, Baxalta, Celgene, Lilly, Merck, Roche. All other authors have declared no conflicts of interest.

477O Bevacizumab (Bev) or cetuximab (Cet) plus chemotherapy after progression with bevacizumab plus chemotherapy in patients with wild-type (WT) KRAS metastatic colorectal cancer (mCRC): Final analysis of a French randomized, multicenter, phase II study (PRODIGE 18)

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Background: Second-line treatment with chemotherapy plus Bev or Cet is now established as a valid option in mCRC. The main objective of this French multicenter, randomized open phase II trial, was to evaluate the Progression Free Survival (PFS) rate at 4 months with chemotherapy plus Bev or Cet in patients with disease progression after Bev plus chemotherapy.

Methods: The main eligibility criterion was disease progression after bevacizumab + 5-FU with irinotecan or oxaliplatin in patients with WT KRAS exon 2 mCRC. Patients were randomized in Arm A (FOLFIRI or mFOLFOX6 plus Bev) or in Arm B (FOLFIRI or mFOLFOX6 plus Cet); the chemotherapy doublet was chosen according to the first line (cross over). Analyses were performed in ITT population. They were repeated on the KRAS + NRAS WT population and in the triple negative population (KRAS, NRAS, and BRAF negative).

Results: From October 2010 to May 2015, 133 patients were included in 25 sites (1 patient ineligible): 85 males (64%), PS 0 (74, 56%), 1 (54, 41%), unknown (4, 3%). The 4-month PFS rate was 80.3% [95%CI (68.0% - 88.3%)] in Arm A and 66.7% [95%CI (53.6% - 76.8%)] in Arm B. Median PFS was 7.1 months in Arm A vs 5.6 months in Arm B ($p = 0.060$). Median OS reached 15.8 months in Arm A vs 10.4 months in Arm B ($p = 0.073$). Tumors samples were collected by a central laboratory and 95 were analysed using the KRAS/BRAF mutation analysis panel kit (KRAS exon 2,3,4 and BRAF V600E) and NRAS mutation detection kit (exons 2,3,4; Entrogen). On the whole, 81 patients were KRAS and NRAS WT (41 in Arm A and 40 in Arm B). Median PFS was respectively 7.8 months and 5.6 months in Arm A and Arm B ($p = 0.076$); median OS was 21.0 months in Arm A vs 10.7 months in arm B ($p = 0.324$). 73 were negative for the 3 genes ($n = 36$ and 37). Their median PFS were 8.2 months in Arm A) vs 5.7 months in arm B ($p = 0.100$). Median OS was 21.1 months vs 12.6 months ($p = 0.365$).

Conclusions: PRODIGE18 study is in favour of bevacizumab continuation beyond progression with chemotherapy cross over in WT RAS mCRC initially treated with first-line Bev plus chemotherapy.

Legal entity responsible for the study: UNICANCER

Funding: Roche

Disclosure: J. Bennouna: Advisory Board for Roche, Boehringer Ingelheim, AstraZeneca, Servier, BMS. S. Hiret: Roche, Boehringer Ingelheim, AstraZeneca. C. Borg: Roche, Sanofi, Servier. O. Bouche: Roche, Merck, Amgen, Lilly, Pierre Fabre, Boehringer Ingelheim, Novartis. E. Francois: Advisory Board: Roche, Merck. F. Ghiringhelli: Roche, Sanofi, Amgen, BMS. J-F. Seitz: Roche, Merck, Sanofi. P. Artru: Roche, Merck, Amgen. A. Adenis: Roche. All other authors have declared no conflicts of interest.

478O Efficacy and safety of Sym004 in refractory metastatic colorectal cancer with acquired resistance to anti-EGFR therapy: Results of a randomized phase II study (RP2S)

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Background: Sym004, a mixture of 2 anti-EGFR monoclonal antibodies (mAbs), was shown to be active in a prior P1/2 trial in refractory mCRC. Due to its unique mode of action, Sym004 was developed for overcoming of acquired resistance to anti-EGFR antibodies.

Methods: 254 patients (pts) were entered to an open label, multinational, 3-arm (1:1:1) RP2S comparing 2 regimens (12 mg/kg [A] or 9 mg/kg loading dose followed by 6 mg/kg [9/6; B]) of weekly Sym004 vs investigator choice (IC) of 5-FU, capecitabine, or best supportive care [C]. Standard eligibility criteria were used; pts were to be refractory to chemotherapy and have responded to, and progressed on anti-EGFR mAb-based therapy; *RAS* exon 2 wild type in tumour archival sample. The study was designed to detect a 3-month (M) improvement in overall survival (OS) (6 vs 9 M) between either Arm A or B and Arm C.

Results: Demographic and baseline parameters were well balanced. The Sym004 adverse event (AE) profile was typical although frequency/severity of dermatologic AEs and hypomagnesemia was higher and GI AEs appeared lower than with approved anti-EGFR mAbs. Arm B was better tolerated than Arm A. OS in the ITT population and exploratory subgroups are presented. The primary outcome of the study was negative due to unexpected outcomes of Arm C. Arm B (9/6 mg dose) was not only better tolerated over 12/6 mg (Arm A), but also was associated with improved survival. Biomarker-specific analyses evaluating pts with double-negative (DN) (no *RAS* mutant allele frequency >20% in circulating tumor [ct]DNA; no *BRAF* V600E) or triple-negative (TN) (DN + no EGFR extracellular domain mutation in ctDNA) mCRC demonstrated markedly prolonged survival and established the 9/6 regimen as well-tolerated and active in DNmCRC (OS increased 3.5 M) and TNmCRC (OS increased 5.5 M).

Conclusions: Although the study was negative in ITT population, treatment with Sym004 was associated with remarkable response when compared with any 4th-line treatment of mCRC. The promising results in the molecularly selected population provide guidance to design a pivotal ctDNA-guided pivotal trial in EGFR inhibitor refractory mCRC.

Clinical trial identification: NCT02083653 or EMR200637-002

Legal entity responsible for the study: Symphogen

Funding: Symphogen

Disclosure: J. Tabernero: Advisory boards: Amgen, Bayer, Boehringer Ingelheim, Celgene, Chugai, Genentech, Lilly, MSD, Merck Serono, Novartis, Pfizer, Roche, Sanofi, Symphogen, Taiho, Takeda. F. Ciardiello: Advisory boards: Roche, Merck, Lilly, BMS, Pfizer, Amgen, Bayer. C. Montagut: Advisory boards: Amgen, Bayer, Merck Serono, Sanofi, Symphogen. C. Ding, T. Tuxen Poulsen, M. Kragh, I.D. Horak: Employee of Symphogen. S. Kopetz: Advisory boards: Amgen, Merrimack, Bayer, Sanofi, Array BioPharma, Genentech, Molecular Match, Symphogen, Guardant Health, EMD Serono, Merck. V. Zagonel: Advisory boards: Celgene, Bayer, Roche, Amgen, Novartis, Pfizer. J. Bennouna: Honoraria: Roche, Boehringer Ingelheim, AstrZeneca, Shire, MSD, BMS; consulting or advisory role: Roche, Boehringer Ingelheim, AstraZeneca, Shire, MSD, BMS. S. Siena: Advisory boards: Amgen, Roche, Bayer, Merck-Serono, Sanofi, Merrimack. A. Falcone: Advisory boards and research grants to Institution: Amgen, Merck, Roche, Bayer, Servier, Lilly, Sanofi. All other authors have declared no conflicts of interest.

479O Consensus molecular subtypes (cms) as predictors of benefit from bevacizumab in first line treatment of metastatic colorectal cancer: Retrospective analysis of the MAX clinical trial

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Background: CMS is a transcriptome-based classification of colorectal cancer (CRC) with prognostic implications, but its association with treatment outcomes, especially in the metastatic setting, remains unknown. We investigated whether CMS classification was predictive of bevacizumab treatment benefit using data from the phase 3 MAX trial. MAX previously reported progression-free survival (PFS) benefit for the addition of bevacizumab (B) to chemotherapy (capecitabine (C) +/- mitomycin (M)) in first line treatment of metastatic CRC.

Methods: Archival tumours from 256 patients (54% of trial population) were available for gene expression profiling using Almac Xcel microarray. Tumours were classified into CMS groups 1 to 4 using previously published methods. We correlated CMS groups with PFS in the MAX trial. The predictive value of CMS was demonstrated as the interaction between CMS and bevacizumab treatment, assessed by Cox proportional hazards model.

Results: After data quality control, primary tumours from 239 patients (51% of trial population) were suitable for survival analysis. Distribution of CMS groups were CMS1 18%, CMS2 48%, CMS3 12%, CMS4 23%. Hazard ratios (HR)(95% CI) of PFS in C vs CB+CBM arms for CMS 1,2,3 and 4 were 0.83 (0.43-1.62), 0.50 (0.33-0.76), 0.31 (0.13-0.75) and 1.24 (0.68-2.25) respectively (test for interaction between CMS and treatment, p = 0.03). CMS remained a significant independent predictor of PFS after adjustment for prognostic factors in a multivariate analysis (p = 0.04).

Table: 478O

Population	Arm A	Arm B	Arm C
ITT N = 254	7.9[a] (6.5, 9.9)[b] N = 83	10.3 (9.0, 12.9) N = 86	9.6 (8.3, 12.2) N = 85
US&EU[c] N = 224	7.7 (6.1, 11.3) N = 75	9.9 (8.0, 12.8) N = 74	8.5 (6.8, 10.2) N = 75
US&EU with biomarker data N = 193	7.7 (5.5, 11.3) N = 70	9.9 (7.1, 12.9) N = 67	8.5 (6.4, 9.9) N = 56)
US&EU with DNmCRC N = 170 (88%)[d]	8.9 (6.2, 12.4) N = 62	11.9 (9.7, 13.8) N = 57	8.4 (6.4, 10.0) N = 51
US&EU with TNmCRC N = 131 (68%)[d]	10.6 (6.8, 13.1) N = 47	12.8 (9.7, 14.7) N = 46	7.3 (6.3, 8.8) N = 38

[a]median survival in M

[b]95% confidence intervals

[c]the subgroup analyses excluded pts due to different medical practice

[d]with biomarker data

Conclusions: In metastatic CRC, CMS 2 and 3 subtypes preferentially benefit from the addition of bevacizumab to chemotherapy, compared to CMS 1 and 4. Validation of these findings in independent cohorts is required. Once validated, CMS classification could be used to guide patient selection for bevacizumab therapy.

Legal entity responsible for the study: Olivia Newton-John Cancer Research Institute, Australia

Funding: Olivia Newton-John Cancer Research Institute, Australia and Australian Gastrointestinal Trials Group (AGITG)

Disclosure: P. Wirapati: Funding: Roche, Bayer and Sanofi for research in predictive biomarker for colorectal cancer. T.J. Price, N. Tebbutt: Advisory boards: Roche All other authors have declared no conflicts of interest.

480O Prognostic value of methylator phenotype in stage III colon cancer treated with oxaliplatin-based adjuvant chemotherapy

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Background: There are conflicting results concerning the prognostic value of the methylator phenotype (CIMP+ for "CpG island methylator phenotype") in non-metastatic colon cancer (CC) patients (pts). We studied this phenotype in stage III CC pts having undergone R0 resection, characterized for MSI, *RAS* and *BRAF* mutation status and treated with adjuvant FOLFOX-based treatment.

Methods: Tumor samples of 1910 pts enrolled in the PETACC-8 adjuvant phase 3 trial were analysed. The method used was methylation-specific PCR where $CIMP^+$ status was defined by methylation of at least three of the five following genes: *IGF2*, *CACNA1G*, *NEUROG1*, *SOCS1* and *RUNX3*. Association between CIMP status and overall survival (OS), disease-free survival (DFS), and survival after relapse (SAR) was assessed by Cox model and adjusted for prognostic factors (including *MSI*, *BRAF* and *RAS* mutation status) and treatment arm (FOLFOX or FOLFOX plus cetuximab). CIMP status was analyzed according to treatment efficacy.

Results: Determination of CIMP status was successful in 1870 pts (98%): 275 (14.7%) tumors were classified $CIMP^+$. Compared to $CIMP^-$ pts, $CIMP^+$ pts were significantly older ($p = 0.002$), with more frequently women ($p = 0.04$). $CIMP^+$ tumors were more frequently right-sided ($p < 0.0001$)), with histopathology grade 3-4 ($p < 0.0001$), pN2 ($p = 0.001$), MSI ($p < 10e\text{-}4$), *BRAF* mutated ($p < 0.0001$) and *RAS* wild-type ($p < 0.0001$). In multivariate analysis, $CIMP^+$ status was associated with shorter OS (HR: 1.4; 95% CI 1.02 – 1.9; $p = 0.04$) and SAR (HR: 1.8; 95% CI 1.2 – 2.6; $p < 0.0004$); but DFS was not significantly different between $CIMP^+$ and $CIMP^-$ pts (HR: 1.1; 95% CI 0.8 1.5; $p = 0.34$). Theses results were independent of the treatment received. No benefit or detrimental effect of cetuximab was observed in $CIMP^+$ patients for OS and DFS.

Conclusions: In a large clinically and molecularly well defined stage III CC population treated with standard adjuvant therapy, methylator phenotype is a prognostic biomarker for OS and SAR. However, no impact of CIMP status on DFS was observed. Finally, we did not find any predictive value of the CIMP status for the efficacy of FOLFOX versus FOLFOX plus cetuximab.

Clinical trial identification: PETACC8 Trial (EuDRACT number: 2005-003463-23)

Legal entity responsible for the study: FFCD

Funding: Merck, Sanofi

Disclosure: J. Taieb: Consulting or/and advisory boards: Merck KGaA, Sanofi, Roche Genentech, Pfizer, Amgen. J. Tabernero: Consulting or/and advisory boards: Amgen, ImClone Systems, Lilly, Millennium, Novartis, Roche/Genentech, Sanofi, Celgene, Chugai Pharma, Taiho Pharmaceutical, Boehringer Ingelheim, Merck KGaA. J-F. Seitz: Grants for consultancy: Celgene, Lilly, Merck, Novartis Oncology, Pfizer, Sanofi, Roche; grants: Roche; payments for development of educational presentations: Amgen, Lilly; travel grants: Ipsen Pharma, Merck. T. Aparicio: Personal grants consultancy: Pierre Fabre; grants: Roche, Amgen; payments for development of educational presentations: Novartis Oncology, Pfizer, Sanofi, Roche; travel grants: Ipsen Pharma, Novartis Oncology, Sanofi, Roche. G. Folprecht: Consulting or/and advisory boards: Merck KGaA, Roche/Genentech, Sanofi-Aventis, Bayer, Lilly, Servier, BMS. C. Lepage: Personal grants for board membership: AAA; grants: Novartis; travel grants: Ipsen Pharma, Amgen, Bayer. J.F. Emile: Honoraria: Amgen, Merck KGaA. P. Laurent-Puig: Consulting or/and advisory boards: Sanofi, Merck KGaA, Amgen, Roche, Genomic Health, Myriad Genetics, Pfizer. All other authors have declared no conflicts of interest.

481PD Sidedness influences prognosis in stage III but not in stage II colon cancer patients receiving an adjuvant therapy: A GISCAD analysis from three randomized trials including 5234 patients

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Background: While in the advanced setting right colon cancer is associated with a worse outcome, this negative prognostic effect has been not definitively demonstrated in the adjuvant setting. We have analyzed the outcome data from 3 large randomized trials (SITAC-1; SMAC and TOSCA) assessing adjuvant therapy in colon cancer patients with stage II and III. Furthermore, since previous trials were not powered to assess the prognostic role of transversum colon cancer, we analyzed this site independently.

Methods: In order to define the prognostic effect of sidedness we assessed three randomized trials of adjuvant therapy (SITAC, 5FU/FA vs control, 821 patients; SMAC, intraportal 5FU vs 5FU/FA, 990 patients; TOSCA, FOLFOX or XELOX three vs six months 3513 patients) carried out in Italy from 1987 to 2013 and including 5324 patients. Survival and disease-free survival, overall and in each trial, were analyzed according to right, transversum and left colon location. Right-sided was considered caecum to hepatic flexure, left-sided splenic flexure to rectum and trasversum hepatic to splenic flexure. Statistical analysis considered all randomized patients according to allocation arm, with available data on putative prognostic factors. Analysis was planned in order to provide overall and by stage results.

Results: 5324 patients were included in this analysis; 2490 patients were males and 2834 females. Median age was 64 years. 2240 patients had a stage II colon cancer and 3084 a stage III. Right tumors were 1573 (30%), trasversum 822 (15%) and left 2929 (55%). Patients characteristics were well balanced among the three trials. In all the 5234 patients DFS was not affected by tumor location (right colon versus left, HR = 1.01; 95% CI = 0.89-1.15) while right tumor was associated to a worse OS compared to left tumor (HR = 1.21; 95% CI = 1.05-1.40) In stage II patients there was no difference in terms of DFS and OS among the three different tumor location while in stage III patients, right colon cancer had a worse outcome both in DFS and OS than left tumor (HR: 1.37 95% CI = 1.16-1.64, $p < 0.001$).

Conclusions: This is the largest analysis demonstrating the prognostic effect of tumor location in colon cancer patients receiving adjuvant chemotherapy. The effect however is present only in stage III but not in stage II colon cancer.

Legal entity responsible for the study: GISCAD Fundation

Funding: None

Disclosure: All authors have declared no conflicts of interest.

482PD Robot-assisted vs laparoscopic vs open abdominoperineal resections for low rectal cancer: Short-term outcomes of a single-center prospective randomized controlled trial

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Background: Currently, robotic surgery for rectal cancer using da Vinci System is common. However, there is almost no clinical trial reported. This randomized controlled trial aims to compare the safety and efficacy of robot-assisted, laparoscopic and open abdominoperineal resection (APR) for low rectal cancer.

Methods: From 2013-09 to 2017-03, patients aged from 18 to 75 years, with low rectal cancer within 5 cm from anal verge, clinical T1 to T3, no distant metastases, were randomly assigned to receive either robot-assisted procedures (RAP), laparoscopic procedures (LAP) or open surgery (OS) for APR in 1:1:1 ratio. The primary endpoint was postoperative complication rate.

Results: Totally 506 patients were enrolled in this study, randomly assigned to RAP (n = 169), LAP (n = 169), and OS (n = 168). Actually, 3 patients refused surgery, 173 finished RAP, 176 finished LAP, and 154 finished OS (including 4 convert from LAP to OS). The open conversion rate was 0 in RAP and 2.4% in LAP, with no significant difference ($P = 0.123$). In per-protocol analysis, no significant difference was observed in tumor location, size, differentiation and pathological TNM stage, among the three groups. RAP had significantly lower postoperative complication rate (10.4%) than both LAP (18.8%, $P = 0.027$) and OS (26.0%, $P < 0.001$). Also, RAP reduced intraoperative hemorrhage (median, 100 ml) than LAP (130 ml, $P < 0.001$) and OS (200 ml, $P < 0.001$). And RAP promoted postoperative recovery, with shorter days to first flatus (1.0 day) than LAP (2.0 day, $P < 0.001$) and OS (3.0 day, $P < 0.001$), shorter days to first automatic urination (2.0 day) than LAP (3.0 day, $P < 0.001$) and OS (3.0 day, $P < 0.001$), and shorter days to discharge (5.0 days) than LAP (6.0 days, $P < 0.001$) and OS (6.0 day, $P < 0.001$). There was no significant difference in resection margin involvement and number of lymph node harvested. More details are shown in the table.

Conclusions: Robot-assisted APR was safe, and reproduce equivalent surgical quality of conventional laparoscopic and open surgery. Also, it provided less injury and faster functional recovery.

Table: 482PD Study results in per-protocol analysis

	RAP (n = 173)	LAP (n = 176)	OS (n = 154)	P value RAP vs. LAP	P value RAP vs. OS
Operating time, min (median, IQR)	205 (200-220)	195 (160-240)	160 (140-180)	0.002	<0.001
Intraoperative hemorrhage, ml (median, IQR)	100 (90-110)	130 (100-150)	200 (120-220)	<0.001	<0.001
Patients with perioperative transfusion, n (%)	0 (0)	2 (1.1)	3 (1.9)	0.499	0.103
Lymph node harvested, n (median, IQR)	16 (13-20)	16 (12-19)	15.5 (13-19)	0.576	0.748
Circumferential resection margin positive, n (%)	1 (0.6)	3 (1.7)	3 (1.9)	0.623	0.346
Days to first flatus (median, IQR)#	1.0 (1.0-2.0)	2.0 (2.0-3.0)	3.0 (2.0-4.0)	<0.001	<0.001
Days to first automatic urination (median, IQR)#	2.0 (2.0-3.0)	3.0 (2.0-4.0)	3.0 (2.0-4.3)	<0.001	<0.001
Days to discharge (median, IQR)#	5.0 (5.0-5.0)	6.0 (6.0-7.0)	6.0 (5.0-7.0)	<0.001	<0.001
Postoperative mortality, n (%)	0 (0)	0 (0)	0 (0)	–	–
Postoperative morbidity, n (%)	18 (10.4)	33 (18.8)	40 (26.0)	0.027	<0.001
Morbidity of Clavien-Dindo Grade III-IV, n (%)	2 (1.2)	6 (3.4)	5 (3.2)	0.284	0.261

RAP: robot-assisted procedures; LAP: laparoscopic procedures; OS: open surgery. IQR: interquartile range. #: excluded patients with complications.

Clinical trial identification: NCT01985698.
Legal entity responsible for the study: Jianmin Xu
Funding: None
Disclosure: All authors have declared no conflicts of interest.

483PD Perioperative chemotherapy with or without cetuximab in patients (pts) with resectable colorectal liver metastasis (CRLM): Mature analysis of overall survival (OS) in the New EPOC randomised controlled trial

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Background: The primary analysis of the New EPOC trial in 2013 demonstrated a shorter progression-free survival (PFS) when cetuximab was added to chemotherapy as perioperative treatment for CRLM. This analysis reports the mature OS data and novel exploratory analyses.

Methods: Pts with KRAS exon 2 wild-type resectable or suboptimally resectable CRLM were randomised to chemotherapy (CT) or chemotherapy and cetuximab (CTX) before and after liver resection. Trial recruitment and use of cetuximab were halted in 2012 on the recommendation of the Data Monitoring Committee.

Results: 128 pts received CT and 129 CTX between Feb 2007 and Nov 2012. At a median follow-up of 69 months (IQR 59-81), 130 events (death from any cause) had been observed. Median OS was shorter for CTX vs CT (p = 0.035) and in contrast to the primary analysis, mature analysis of PFS was not significantly different (p = 0.291). There were numerically more multi-site progressions in CTX (n = 17/83, 20.5%) than CT (n = 8/78, 10.3%) pts and survival post-progression (PPS) was particularly poor for CTX pts (p = 0.014). Predefined subgroup analyses demonstrated the adverse effect of CTX was in pts conventionally thought to have good prognostic features. Whilst OS was the same for responders and non-responders on CT, it was improved for responders vs non-responders on CTX.

Table: 483PD

	Median survival (months)		HR	95%CI
	CT	CTX		
PFS	23.9	15.5	1.17	0.87-1.57
PPS	35.4	23.5	1.60	1.10-2.33
OS				
All	81.0	55.4	1.45	1.02-2.05
OS by pre-operative response				
Yes	81.1	60.7	1.40	0.89-2.20
No	79.9	34.5	2.19	1.22-3.95
≥4 metastases/poor differentiation of primary/N2 disease				
Yes	59.2	58.3	0.95	0.61-1.51
No	not reached	45.8	2.37	1.39-4.06

Conclusions: In the context of perioperative therapy for resectable CRLM CTX confers a shorter OS and survival post progression compared to CT. This detriment is in those with conventionally favourable prognostic features suggesting that cetuximab induces adverse biology in some pts, the biomarker profile of whom is being investigated. Response to CT alone does not improve OS compared to non-responders, suggesting conferred benefit is adjuvant not neoadjuvant.

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Legal entity responsible for the study: University Hospital Southampton NHS Foundation Trust
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484PD Analysis of tumor PD-L1 expression and biomarkers in relation to clinical activity in patients (pts) with deficient DNA mismatch repair (dMMR)/high microsatellite instability (MSI-H) metastatic colorectal cancer (mCRC) treated with nivolumab (NIVO) + ipilimumab (IPI): CheckMate 142

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Background: In the CheckMate 142 trial (NCT02060188), NIVO + IPI demonstrated manageable safety and clinical activity characterized by an investigator-assessed objective response rate (ORR) of 55%, disease control rate (DCR; defined as CR + PR + SD ≥ 12 wk) of 79%, and encouraging survival benefit (6-mo PFS and OS rates:77% and 89%) in pts with dMMR/MSI-H mCRC (Andre T, et al. ASCO 2017). Here, we report biomarker analyses in pts who received NIVO + IPI in the CheckMate 142 study.

Methods: Pts with dMMR/MSI-H mCRC who progressed on or were intolerant of ≥ 1 prior line of therapy received NIVO 3 mg/kg + IPI 1 mg/kg Q3W × 4 doses followed by NIVO 3 mg/kg Q2W. Tumor anti-programmed death ligand 1 (PD-L1) expression was assessed using the Dako 28-8 pharmDx assay. PD-L1 positivity was defined as ≥ 1% cell membrane staining of any intensity. *BRAF* and *KRAS* mutation statuses were determined by investigators per local guidelines. Characterization of Lynch syndrome as present or absent was based on past medical history from clinical records. ORR per investigator was determined per RECIST v1.1.

Results: Tumor PD-L1 expression and *BRAF/KRAS* statuses were assessed in 84 pts. ORR and DCR by PD-L1, BRAF/KRAS mutational status, and clinical history of Lynch syndrome are reported in the Table below.

Conclusions: Confirmed responses with NIVO + IPI were observed in pts with dMMR/MSI-H mCRC who were PD-L1 expressors and non-expressors, as well as across *BRAF* and *KRAS* mutational status. Responses were also observed in pts with or without a history of Lynch syndrome. These results are consistent with previously reported biomarker analyses of the NIVO monotherapy cohort.

Table: 484PD

Pts, n (%) [95%CI]	dMMR/MSI-H mCRC N = 84 Pts With ≥ 6 Mo of Follow-Up	
	ORR	DCR
Tumor PD-L1 expression*		
≥1% (n = 16)	9 (56) [29.88, 80.25]	12 (75) [47.62, 92.73]
<1% (n = 50)	27 (54) [39.32, 68.19]	39 (78) [64.04, 88.47]
Mutation status†		
BRAF mutant (n = 21)	10 (48) [25.71, 70.22]	16 (76) [52.83, 91.78]
KRAS mutant (n = 30)	19 (63) [43.86, 80.07]	26 (87) [69.28, 96.25]
BRAF/KRAS wild type (n = 22)	13 (59) [36.36, 79.29]	17 (77) [54.63, 92.18]
Clinical history of Lynch syndrome‡		
Yes (n = 27)	20 (74) [53.72, 88.89]	22 (81) [61.92, 93.70]
No (n = 25)	12 (48) [27.80, 68.69]	19 (76) [54.87, 90.64]

*18 pts had no quantifiable PD-L1 expression at baseline;
†11 pts had unknown *BRAF/KRAS* status at baseline;
‡32 pts had unknown Lynch syndrome status at baseline

Clinical trial identification: Clinical Protocol CA209142. The release date 18-Nov-2013.

Legal entity responsible for the study: Bristol-Myers Squibb

Funding: Bristol-Myers Squibb

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485PD Randomized phase III study of adjuvant chemotherapy with S-1 versus capecitabine in patients with stage III colorectal cancer: Updated results of Japan Clinical Oncology Group study (JCOG0910)

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Background: We demonstrated that the second planned interim analysis (median follow-up, 23.7 months) of the JCOG0910 failed to show non-inferiority of adjuvant S-1 to capecitabine in disease-free survival (DFS: relapse, second malignancy, death are events) at ASCO2015 (abstract # 3512), and the results were opened by the recommendation of JCOG Data and Safety Monitoring Committee. We updated the follow-up data to confirm the conclusion at the interim analysis.

Methods: Key eligibility criteria were: stage III, colorectal adenocarcinoma except for lower rectal cancer, R0 with D2/3 lymph node dissection. Patients were randomized to 8 courses of capecitabine (1,250 mg/m^2 twice daily, days 1–14, every 3 weeks) or 4 courses of S-1 (40 mg/m^2 twice daily, days 1–28, every 6 weeks). Primary endpoint was DFS. Planned sample size was 1,550 in order to provide 80% power with a non-inferiority margin at a hazard ratio (HR) of 1.24 and 1-sided $\alpha = 0.05$. This trial is registered with UMIN-CTR, #UMIN000003272.

Results: 1,564 patients were randomized to capecitabine (n = 782) or S-1 (n = 782). At the end of the follow-up period of 3 years, 69% of required events (368/535) were observed, with a median follow-up for all randomized patients of 4.13 years, 3-year DFS was 81.7% (95% CI, 78.8 - 84.2%) in capecitabine and 78.3% (75.2 - 81.0%) in S-1. The HR of DFS was 1.22 (95% CI, 1.00–1.50) and the non-inferiority of S-1 was not demonstrated (P for non-inferiority = 0.448). Three-year relapse-free survival (RFS: relapse, death are events) was 84.6% in capecitabine and 81.5% in S-1. The HR of RFS was also 1.21 (95% CI, 0.96–1.53). Three-year overall survival (OS) was 96.3% in capecitabine and 95.4% in S-1. The HR of OS was 1.18 (95% CI, 0.83–1.68). In the subgroup analyses, no significant interactions were identified between the major baseline characteristics.

Conclusions: These updated results confirmed that S-1 could not be demonstrated to be non-inferior to capecitabine in DFS. Adjuvant capecitabine remains the standard treatment and S-1 is not recommended.

Clinical trial identification: #UMIN000003272

Legal entity responsible for the study: Japan Clinical Oncology Group

Funding: National Cancer Center and Ministry of Health, Labour and Welfare of Japan

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486O Sequential first-line therapy of metastatic colorectal cancer (mCRC) starting with fluoropyrimidine (FP) plus bevacizumab (BEV) vs. initial FP plus irinotecan (IRI) and BEV: German AIO KRK0110 (ML22011) study

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Background: The AIO KRK-0110 study compares a sequential application of FP+ BEV followed by IRI+ FP+ BEV at first progression (arm A) vs. initial FP+ IRI+ BEV (arm B) in patients (pts) with untreated mCRC.

Methods: The primary efficacy-endpoint was time-to-failure of strategy (TFS). The non-inferiority margin was a 90% confidence interval of a hazard ratio (HR) of 0.8 (Power 70%, $\alpha = 0.05$). Secondary endpoints of the study included response rate, progression-free survival (PFS), overall survival (OS), efficacy in molecular subgroups and quality of life (EORTC QLQ C30).

Results: The full analysis set (FAS) consists of 421 pts (212/209 Arm A/B), median age was 71 years. The primary endpoint (TFS) was not met (HR: 0.86 (0.73-1.02)). Concerning TFS, patients with *RAS/BRAF* wild-type (WT) mCRC appeared to have significant benefit from initial irinotecan while this was not observed in patients with mutant (MT) *RAS* or *BRAF*. A Cox model interaction test for study arm and *RAS*-status was significant (P = 0.03). PFS and OS were consistent with TFS (see table for details). Objective response rate favored the initial irinotecan-arm (36.8% vs 53.6%, P = 0.005). Quality of life (global health, physical functioning, etc) was not substantially different between both study arms at baseline and end of treatment.

Conclusions: In this trial comprising a more elderly population, non-inferiority for TFS of initial FP+ BEV as compared to FP+ IRI+ BEV was not shown. In detail, sequential therapy was inferior in pts with *RAS/BRAF*-WT mCRC and cannot be recommended. However, sequential bevacizumab-based therapy could be discussed as an option in elderly pts with *RAS MT* mCRC. Conclusions on *BRAF* mutant tumors are limited by sample size.

Clinical trial identification: NCT01249638

Legal entity responsible for the study: Hospital of the University of Munich (LMU)

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Table: 486O

Population	PFS-1		TFS		OS	
	mo. (95%CI)	Hazard ratio P-value	mo. (90%CI)	Hazard ratio P-value	mo. (95%CI)	Hazard ratio P-value
FAS						
Arm A (N = 212)	8.0 (6.9-9.9)	0.70 (0.57-0.85)	9.6 (8.6-10.6)	0.86 (0.73-1.02)	21.9 (20.2-25.0)	0.84 (0.66-1.06)
Arm B (N = 209)	9.9 (8.7-10.9)	P < 0.001	9.9 (8.8-10.6)	P = 0.16	23.5 (20.9-27.9)	P = 0.14
RAS/BRAF WT						
Arm A (N = 79)	8.4 (7.1-9.8)	0.49 (0.35-0.69)	9.1 (7.8-10.9)	0.61 (0.46-0.82)	25.2 (20.8-29.8)	0.58 (0.38-0.89)
Arm B (N = 79)	12.6 (10.1-15.1)	P < 0.001	12.6 (10.4-14.3)	P = 0.005	32.2 (26.1-46.4)	P = 0.01
RAS MT						
Arm A (N = 97)	8.1 (6.0-10.2)	0.87 (0.65-1.17)	10.0 (8.5-11.5)	1.09 (0.81-1.46)	21.3 (19.6-23.0)	0.92 (0.65-1.29)
Arm B (N = 97)	9.3 (8.2-10.5)	P = 0.34	9.4 (8.0-10.7)	P = 0.58	23.2 (18.1-28.4)	P = 0.62
BRAF MT						
Arm A (N = 12)	5.8 (0.0-12.1)	1.43 (0.59-3.47)	6.9 (4.2-10.2)	1.62 (0.76-3.47)	12.4 (10.2-20.2)	1.50 (0.60-3.76)
Arm B (N = 10)	4.5 (2.8-6.2)	P = 0.44	4.5 (3.1-8.4)	P = 0.29	7.8 (4.7-13.5)	P = 0.38

487P International comparison of stage-specific treatment of and survival from colorectal cancer: England, Norway and Sweden, 2010-2012

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Background: Colorectal cancer patients in England have worse outcomes than patients diagnosed in other high-income countries with similar healthcare coverage. We aim to compare clinical characteristics and survival of colorectal cancer patients in England, Norway and Sweden to understand whether differences in stage and treatment could help to explain international differences in survival.

Methods: Information on patients aged 15-99 years diagnosed with primary malignant tumours of the colon and rectum in England, Norway and Sweden during 2010-2012 was extracted from national cancer registration and/or specialised colorectal cancer registry data. Six-month, one-year and two-year net survival was estimated for each country, stage at diagnosis, and surgical treatment status.

Results: There were 93,125 colorectal cancer diagnoses in England, 11,155 in Norway, and 17,925 in Sweden during the time period. Stage was more advanced in colon than in rectal tumours. England had slightly poorer stage distribution, and a higher proportion of missing stage, than Norway and Sweden. Overall, 64.1% of colorectal cancer patients diagnosed in England, 68.8% diagnosed in Norway and 70.3% diagnosed in Sweden had evidence of receiving potentially curative surgery. These surgically treated patients were on average younger in England than in Norway and Sweden, in each stage category. Stage-specific net survival was generally highest in patients in Sweden and lowest in those in England. The survival deficit of English patients was particularly large compared to similar patients in the other countries among those diagnosed with advanced disease and/or who did not receive potentially curative surgery.

Conclusions: Stage-specific survival from colorectal cancer in England was lower than in Norway and Sweden. This survival deficit may be partly explained by the higher proportion, and lower survival, of patients who did not receive potentially curative surgery in England. The different proportions of missing data may somewhat affect the comparability of the results; however these remain informative.

Legal entity responsible for the study: Cancer Survival Group, London School of Hygiene and Tropical Medicine

Funding: Cancer Research UK

Disclosure: All authors have declared no conflicts of interest.

488P Early postoperative PET-CT in patients with pathological stage III colon cancer may change their outcome: Results from a large single institution study

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Background: Staging of patients (pts) with pathological stage III colon cancer (CC) is currently suboptimal; many pts still recur despite an unremarkable preoperative staging. We previously reported that early postoperative PET-CT can alter the stage and management of up to 15% of pts with high risk stage III CC and later reported also encouraging preliminary results in a larger cohort of consecutive pts with stage III CC, in which staging and management were altered in 14.5%. The aim of the current study was to expand the previous one to a larger cohort and to evaluate the actual impact of early postoperative PET-CT on pts outcome.

Methods: A Retrospective study of all consecutive pts with stage III CC who were treated at our institution and underwent early postoperative PET-CT between 2007-2016. Demographic and clinicopathological data were retrieved. Statistical analyses were done using standard methods.

Results: 348 pts, 166 (47.7%) males, with a median age of 66 years (range, 29-92), were included. Pathological stage was IIIA, IIIB and IIIC in 21(6%), 254 (73%) and 73 (21%) pts, respectively. The median number of lymph nodes examined and of positive ones were 14 (range, 3-54) and 2 (range, 0-32), respectively. High FDG-uptake was noted in 95 (27.3%) pts, including 23 (6.6%) with clear postoperative changes and 18 (5.2%) with a false positive uptake, of whom 6 underwent invasive diagnostic procedures. PET-CT results modified the management of 52 pts (14.9%) who were found to have true positive findings: 44 (12.6%) with overt metastatic disease and 8 (2.3%) with a second primary tumor. At a median follow-up of 45.6 months, the estimated 5y disease-free survival for true stage III pts was 81.9% and the 6y overall survival of the entire cohort was 76.4%. Interestingly, of the 44 pts found to be metastatic, 12 (27.3%) underwent curative treatments and 8 (66.7%) of those remain free of disease, with a median follow-up of 64.7 months.

Conclusions: In this large cohort, early postoperative PET-CT changed the staging and management of 14.9% of pts with resected stage III CC, with encouraging outcome results. We are conducting a prospective trial to further evaluate this strategy.

Legal entity responsible for the study: Davidoff Cancer Center, Rabin Medical Center

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Disclosure: All authors have declared no conflicts of interest.

489P Role of body composition in early stage colorectal cancer (CRC) outcomes

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Background: CRC is the 3rd most common cancer worldwide. Novel prognostic factors are needed to allow practitioners to stratify and personalize treatment and surveillance options to patients (pts). The objective of this study was to determine associations between body composition and disease-specific outcomes in early stage CRC. We hypothesized that pts with sarcopenia or reduced muscle radiodensity (SMD) at time of surgery will have worse overall outcomes, specifically in their 5-year overall (OS) and disease free survival (DFS). Also, that pts with accelerated skeletal muscle loss at their 2-year surveillance computed tomography (CT) scan will have higher recurrence rates.

Methods: This is a retrospective cohort study of early stage (I-III) CRC from 2007-09. We excluded any pt without analyzable or preoperative CT scan or if a prior diagnosis of CRC. Routine CT imaging was used to measure skeletal muscle (SMA). Total body SMA was normalized for height (skeletal muscle index, SMI). An SMI <52.4 cm^2/m^2 and <38.5 cm^2/m^2 was used as a cutoff for sarcopenia in men and women, respectively. Mean muscle radiodensity in HU was obtained as a measure of myosteatosis.

Results: A total of 2049 pts were identified, of which 1455 had available, analyzable imaging. The cohort was 59% male. The median age was 67 yrs with over 50% older than 65. Most pts presented with stage II-III disease (39%, 50%, respectively). The prevalence of sarcopenia was 45.0% in females and 56.2% in males, with an average SMI of 40 and 51 cm^2/m^2, respectively. Average SMD was 31.5 HU for females and 33.2 HU for males. Pts with disease recurrence had a significantly lower SMI (49 vs. 42 cm^2/m^2, $p < 0.001$). Pts with recurrence also had lower HU (33.3 vs. 30.3 HU, $p = 0.001$). The median time to recurrence was 538 days and average length of follow up was 5 yrs. Data collection and analysis is currently ongoing. We anticipate that pts with disease recurrence within 5 yrs of diagnosis will have a significantly faster rate of muscle loss.

Conclusions: Our study demonstrates for the first-time body composition's ability to predict recurrence of a solid tumor after curative surgery. Pts with reduced overall SMI and SMD had increased risks of disease recurrence. These findings if validated may allow better stratification of treatment and surveillance of CRC pts.

Legal entity responsible for the study: University of Alberta

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Disclosure: All authors have declared no conflicts of interest.

490P North Japan multicenter phase II study of FOLFOX as adjuvant chemotherapy for stage III colon cancer (NORTH/HGCSG1003): Analysis of tumor location

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Background: FOLFOX is the standard adjuvant chemotherapy for resected stage III colon cancer. MOSAIC trial was performed outside of Japan, and we conducted a phase II study (NORTH/HGCSG1003) to assess the efficacy and safety of FOLFOX as adjuvant chemotherapy for Japanese patients (pts) with resected stage III colon cancer (UMIN ID: 000004590). In 2017 ASCO-GI, Shichinohe, et al. reported that the 3-year disease-free survival rate (3y-DFS rate) as the primary endpoint was 75.2%. Recent analysis of pts with metastatic colorectal cancer has shown that primary tumor location correlates with different outcome. However, with regard to adjuvant chemotherapy for resected stage III colon cancer, there are few reports of treatment outcomes by primary tumor location.

Methods: This phase II study enrolled patients with resected stage III colon cancer. Patients received 12 cycles of FOLFOX4 or mFOLFOX6. We analyzed 264 patients registered in this phase II study. This study was analyzed by CTCAE v4.0 for adverse events (AEs) and Kaplan-Meier method for DFS and relapse-free survival (RFS). To compare with right-sided tumor (RT: Cecum to Transverse colon) and left-sided tumor (LT: Descending colon to Rectosigmoid colon), Fisher's exact test was used in terms of patient characteristics, AE, and Log-rank test was used in DFS and RFS.

Results: Patients with RT and LT were 93 and 171, respectively. The patient characteristics between RT and LT were generally balanced except for pathological stage (IIIA/IIIB/IIIC; 6.4/78.5/15.1% in RT, 18.1/71.9/10.0% in LT; $p = 0.019$), number of harvested lymph nodes (median; 23 in RT, 16 in LT; $p = 0.001$), and perforation (0% in RT, 4.1% in LT; $p = 0.054$). There were no significant differences in AEs ($\geq$Grade 3) and relative dose intensity between RT and LT. 3y DFS rate was 75.9% in RT and 73.8% in LT (HR 1.122, $p = 0.636$). 3y RFS rate was 77.6% in RT and 76.0% in LT (HR 1.193, $p = 0.490$).

Conclusions: There were no significant differences between RT and LT in the efficacy and safety of FOLFOX as adjuvant chemotherapy. This analysis suggested that FOLFOX might provide benefit for resected stage III patients regardless of primary tumor location.

Clinical trial identification: UMIN000004590

2011/01/15

Legal entity responsible for the study: Non-profit organization: Hokkaido Gastrointestinal Cancer Study Group

Funding: Non-profit organization: Hokkaido Gastrointestinal Cancer Study Group

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491P Factors predicting adherence to a tailored-dose adjuvant treatment based on geriatric assessment in elderly people with colorectal cancer: A prospective study

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Background: Selecting elderly people with colorectal cancer (CRC) for adjuvant chemotherapy is challenging. Comprehensive geriatric assessment (CGA) can help by classifying them according to their frailty profile. The supposed benefit of chemotherapy is based on the rate of treatment adherence. This study evaluated tolerance and adherence to tailored-dose adjuvant therapy based on CGA in a cohort of older patients with high-risk stage II and stage III CRC.

Methods: Prospective study in 193 consecutive patients aged 75 or older. Based on CGA results, we classified patients as fit, medium-fit, or unfit, administering standard therapy, adjusted treatment and best supportive care, respectively. We recorded planned chemotherapy, toxicity, and completion of the treatment. A logistic multivariate analysis was carried out.

Results: Seventeen (15%) of the 141 candidates for chemotherapy (n = 86 fit and n = 55 medium-fit) refused treatment; associated factors included polypharmacy (odds ratio [OR] 5.34, 95% confidence interval [CI] 1.55, 18.40) and rectal location (OR 5.61, CI95%, 1.45, 21.49). Of the 105 patients receiving chemotherapy, 20 (27%) fit and 4 (13%) medium-fit patients experienced grade 3-4 toxicity (p = 0.11) without association to explanatory variables. About 55% of patients treated with chemotherapy received at least 80% of the planned dose (55% fit and 58% medium-fit patients; p = 0.7). Factors associated with completion of chemotherapy were the absence of toxicity (OR 7.67, CI95% 2.41, 24.43) and social support (OR 2.29, CI95% 0.08, 1.04).

Conclusions: CGA is useful for selecting elderly patients for adjuvant chemotherapy, adapting the dose to their frailty profile, and identifying adherence-related factors amenable to modification through CGA-based interventions.

Legal entity responsible for the study: Institut Català d'Oncologia

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Disclosure: All authors have declared no conflicts of interest.

Table: 491P

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Analysis	**Treatment refusal n = 141**			
Age	1.58 (0.53, 4.67)	0.41	1.17 (0.95, 1.445)	0.15
Sex	0.71 (0.23, 2.15)	0.54		
Cancer site Colon Rectum	1 3 (1.04, 8.62)	0.04	1 5.61 (1.45, 21.49)	**0.01**
Tumor Stage II III	1 0.51 (0.17, 1.54)	0.23		
Polypharmacy	4.01 (1.39, 11.56)	0.01	5.34 (1.55, 18.40)	**0.01**
Weight loss >10%/6 months	0.8 (1.66, 3.86)	0.78		
Yesavage	1.20 (0.43, 3.40)	0.73		
Social support	1.71 (0.50, 5.92	0.39		
VES-13 ≥3	5.78 (1.91, 17.47)	<0.001	3.21 (0.75, 13.79)	0.12
Oncogeriatric group Fit Medium-fit	1 3.41 (1.19, 9.77)	0.02	1 2.86 (0.65, 12.50)	0.16
Analysis	**Toxicity grade ≥3 n = 105**			
Age	1.63 (0.61, 4.40)	0.33		
Sex	1.28 (0.51, 3.25)	0.60		
Cancer site Colon Rectum	1 1.17 (0.40, 3.37)	0.78		
Tumor stage II III	1 0.46 (0.16, 1.26)	0.12		
Polipharmacy (>5 medications)	1.26 (0.43, 3.65)	0.68		
Weight loss >10%/6 months	0.48 (0.10, 2.27)	0.34		
Yesavage	0.99 (0.40, 2.48)	0.99		
Social support no	1.68 (0.52, 5.41)	0.52		
VES-13 > 3	0.74 (0.65, 0.83)	0.13		
Oncogeriatric group Fit (standard dose) Medium-fit (adapted dose)	1 0.4 (0.12, 1.29)	0.12		
Analysis	**Completion ≥ 80% of planned dose n = 105**			
Age (younger)	2.72 (1.10, 6.72)	0.03	1.13 (0.95, 1.35)	0.16
Sex (male)	2.12 (0.95, 4.78)	0.07	0.50 (0.20, 1.26)	0.14
Cancer site Colon Rectum	1 0.85 (0.34, 2.14)	0.73		
Tumor stage II III	1 1.09 (0.42, 2.72)	0.90		
Polypharmacy	2.31 (0.90, 5.95)	0.08	0.50 (0.20, 12.6.)	0.09
Weight loss >10%/6 months	1.09 (0.37, 3.27)	0.87		
Yesavage	1.08 (0.50, 2.34)	0.85		
Social support	3.24 (1.04, 10.11)	0.04	3.44 (1.01-12.31)	**0.05**
VES-13 ≥3	0.92 (0.29, 2.85)	0.88		
Oncogeriatric group Fit (standard dose) Medium fit (adapted dose)	1 0.85 (0.36, 1.98)	0.71		
Toxicity	7.19 (2.43, 21.32)	< 0.001	0.13 (0.04,0.42)	**0.001**

492P Benefits of upfront primary tumour resection (UPTR) according to sidedness in mCRC: Retrospective analyses of TTD MACRO-2 and PLANET randomised trials

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Background: UPTR remains controversial in the initial management of unresectable asymptomatic mCRC patients (pts), whereas right sidedness is a bad prognostic factor.

Methods: Retrospective pooled analysis of KRAS WT mCRC pts treated with 1st line EGFR inhibitors (EGFRI) + chemotherapy (CT) from two phase II randomised trials (MACRO-2 & PLANET). We analysed UPTR effect on overall survival (OS) and progression free survival (PFS) by tumour sidedness (right/left) and stage (I-III/IV) at diagnosis. All stage I-III pts underwent UPTR at diagnosis as standard procedure.

Results: 260 pts were included in the analysis (Table). In pts with stage IV at diagnosis, UPTR was associated with a better OS, although differences were only significant in right sided tumours (mOS (m): 20.9 vs 10.6; HR non-UPTR vs UPTR 2.1 (1.0, 4.3); P = 0.038). Conversely, left sided tumours had a significantly better OS vs right sided tumours regardless of UPTR: UPTR HR 0.4 (0.2, 0.8); P = 0.006; no UPTR HR 0.2 (0.1, 0.4); P < 0.0001. In pts with stage I-III at diagnosis (all UPTR), there were no differences in OS according to sidedness. After UPTR, OS was significantly higher in stage I-III tumours vs stage IV only in right sided tumours. Similar results were observed for PFS.

Conclusions: In mCRC *KRAS* WT pts treated in 1st line with EGFRI + CT, UPTR seemed to improve outcomes particularly in right sided tumours. Table: 492P Median (95%CI) OS and PFS

Table: 492P

	Right		Left	
	UPTR	**No UPTR**	**UPTR**	**No UPTR**
Stage I-III at diagnosis, N	9		31	
OS(m)	34.9		28.9	
	(30.6 -)		(17.6 -)	
HR left vs right			1.5 (0.6, 4.1)	
p			0.430	
PFS(m)	14.3		10.8	
	(8.5, 19.8)		(7.6, 13.9)	
HR left vs right			1.7 (0.7, 4.2)	
p			0.281	
Stage IV at diagnosis, N	18	24	78	100
OS(m)	20.9	10.6	36.9	26.5
	(5.9, 34.2)	(6.3, 11.8)	(25.3, 45.8)	(20.7, 32.0)
HR No UPTR vs UPTR		2.1 (1.0, 4.3)		1.4 (1.0, 2.0)
p		0.038		0.088
UPTR				
HR left vs right			0.4 (0. 2, 0.8)	
p			0.006	
HR Stage IV vs Stage I-III	4.4 (1.4, 13.9)		1.0 (0.6, 1.8)	
p	0.019		0.931	
No-UPTR				
HR left vs right				0.2 (0.1, 0.4)
p				<0.0001
PFS(m)	7.2	4.0	9.9	9.8
	(1.9, 14.8)	(3.5, 6.5)	(7.4, 12.8)	(8.4, 11.7)
HR No UPTR vs UPTR		2.36 (1.0, 5.6)		1.02 (0.7, 1.5)
p		0.049		0.932
UPTR				
HR left vs right			0.6 (0.3, 1.2)	
p			0.123	
HR Stage IV vs Stage I-III	3.5 (1.1, 11.1)		1.1 (0.7, 1.8)	
p	0.036		0.745	
No-UPTR				
HR left vs right				0.27 (0.2, 0.5)
p				<0.0001

Clinical trial identification: MACRO-2 trial: NCT01161316 - PLANET trial: NCT00885885

Legal entity responsible for the study: Spanish Cooperative Group for the Treatment of Digestive Tumors (TTD)

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493P Surgical quality and the impact of liver resection on outcome in the new EPOC study

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Background: The New EPOC study demonstrated a shorter progression-free survival (PFS) with the addition of cetuximab to chemotherapy for operable colorectal liver metastasis. The combination of a liver resection with EGFR inhibition is unique to this study. This analysis explores both surgical quality and the impact of volume of liver resected on outcome.

Methods: Data is presented for 263/271 patients (early study withdrawals excluded). Details of surgery were completed by the operating or lead surgeon in 19 UK specialist centres. The report of no residual tumour in the pathological specimen was queried in each case. Volume of liver resected was estimated and patients divided into tertiles (tertile 1: ≤20.5%, tertile 2 20.6-44.1%, tertile 3: 44.2-84.8%) to investigate association with PFS.

Results: Operations were performed on 233/263 patients (118 chemo alone CT, 115 chemo and cetuximab CTX) of which 205 (108 CT, 97 CTX) underwent resection. A further 18 had surgery that included ablation (6 CT, 12 CTX). 155 had major resections (87 CT, 68 CTX) and the median estimated volume of total liver volume resected was the same in both groups (CT 27.8% IQR 17.0-63.4, CTX 27.8% 17.4-63.4). In the CT group PFS was significantly associated with the volume of liver resected (tertile 1 median PFS not reached, tertile 2 28 months, tertile 3 18.7 months, p = 0.02). Those with a smaller resection volume (tertile 1, ≤20%) appeared to have a shorter PFS with cetuximab (median PFS for CT not reached, CTX 15.2 months, HR 2.15 95%CI 1.00-4.57 p = 0.06). By contrast those with a larger volume of liver resected (tertiles 2 & 3) had similar outcomes irrespective of the use of cetuximab (median PFS for CT 20.2 months, CTX 16.9 months, HR 1.06 95%CI 0.65-1.71 p = 0.83). When analysis was restricted to just those with a R0 resection the shorter PFS with cetuximab persisted (HR 1.68 95% CI 1.04-2.71 p = 0.035). Examination of the pathological specimen revealed no residual tumour in 22 patients (14 CT, 8 CTX) of whom 8 have disease progression (6 CT, 2 CTX).

Conclusions: These exploratory analyses suggest the technical aspects of surgery are similar between the treatment groups and that those patients having smaller volume resections may be disadvantaged by the addition of cetuximab.

Clinical trial identification: ISRCTN 22944367

Legal entity responsible for the study: University Hospital Southampton NHS Foundation Trust

Funding: Cancer Research UK

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494P Short-term clinical outcome from a randomized controlled trial of the conventional technique versus the no-touch isolation technique for primary tumor resection in patients with colon cancer: Japan Clinical Oncology Group study JCOG1006

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Background: The no-touch isolation technique (NTIT) aims to reduce cancer cells flowing from the primary tumor site to liver and other organs by first ligation of blood vessels that feed the primary tumor. A previous randomized controlled trial (RCT) failed to prove its efficacy with statistical significance because of insufficient sample size and many patients being lost to follow-up. We conducted a phase III trial to confirm the superiority of NTIT in patients with cT3/T4 colon cancer.

Methods: Eligibility criteria included histologically proven colon cancer; tumor located in the cecum, ascending, transverse, descending, sigmoid or rectosigmoid colon; T3 or T4; N0-2 and M0; patients age 20-80 years. Patients were randomized preoperatively to either conventional technique (CoT) arm or NTIT arm. Patients with pathological stage III received adjuvant chemotherapy with capecitabine. The primary endpoint was disease-free survival (DFS), and planned sample size was 850 to detect 6% difference in 3-year DFS with one-sided alpha of 5% and power of 80%. Short-term clinical outcomes were compared between the arms. (UMIN-CTR: UMIN000004957).

Results: A total of 853 patients were randomized (CoT: 427, NTIT: 426) between January 2011 to November 2015. Conversion to CoT was needed for 5 (1.2%) patients in NTIT arm. Regarding surgical procedure, there were no differences in operative time (median 172 min: CoT, 178 min: NTIT, p=0.43), and in blood loss (median 69 ml: CoT, 77 ml: NTIT, $p = 0.92$). Postoperative complications and time to pass first flatus (median 2 days: CoT, 2 days: NTIT, $p = 0.64$) did not differ between the arms. There was no hospital death in both arms. Regarding radicality of surgery, there were no differences in D3 lymph node dissection rate (96.3%: CoT, 96.2%: NTIT) and pathological R0 resection rate (98.6%: CoT, 96.7%: NTIT).

Conclusions: Operative quality, postoperative course, radicality, morbidity and mortality are similar in two arms. The primary analysis planned for 2019 is pivotal to prove superiority of NTIT to CoT in term of DFS.

Clinical trial identification: UMIN-CTR: UMIN000004957

Legal entity responsible for the study: National Cancer Center

Funding: National Cancer Research and Development Fund (26-A-4, 29-A-3)

Disclosure: All authors have declared no conflicts of interest.

495P Prognostic impact of tumor deposits in colorectal cancer with lymph nodes metastasis

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Background: Tumor deposit (TD) was an important clinical characteristic associated with adverse prognosis in colorectal cancer (CRC), reported in 4.9%-41.8% CRC patients. The frequent alteration of TDs definition and category criteria in the recent 4 versions of TNM staging system make it controversial. There are several points that are not clear in the latest TNM classification regarding the coexistence of TDs and LNMs and the comparison of the prognosis value between TDs and LNMs.

Methods: Two large-scale cohorts were collected for optimally categorizing TDs with LNM in the tumor stage. The first cohort was from the SEER database involving 65,537 patients between 2011 and 2013. The second cohort was from Fudan University Shanghai Cancer Center (FUSCC) involving 2853 patients between 2010 and 2014.

Results: TDs were observed in 6.32% of patients in SEER cohort and 14.7% in FUSCC cohort. A significantly reduced overall survival was observed for TDs in LNM positive CRC patients (hazard ratio [HR], 1.65; 95% CI, 1.54 to 1.76) in SEER cohort. Prognosis became worse as the number of LNMs increasing, but there was no significant difference in different numbers of TDs in the SEER cohort and FUSCC cohort. Therefore, whether TDs exist or not was the main point. Further analysis combining TDs with LNM shows that there is no considerable difference in the impact on overall survival between N1 and N1c, between N1 with TDs (N1TD) and N2. The 3-year survival rate was 82.3%, 72.0%, 69.9%, 55.7%, 52.1%, 39.4% for N0, N1, N1c, N1TD, N2 and N2 with TDs (N2TD) respectively in SEER cohort. Similar results were observed in the FUSCC cohort.

Conclusions: TD should not be considered as LNM, because they have different survival impact based on our study results. TDs and LNMs could be integrated into a modified pathological N category including 6 subtypes (N0, N1c, N1, N1TD, N2 and N2TD). Among these subtypes, the prognosis of N1c and N1 was similar which means that the revision concerning TDs in the 7th TNM staging system is adequate to predict the pN1c patients' outcome. For the condition of TDs and LNMs coexistence, the prognosis of N1TD and N2 was similar and the prognosis of N2TD was the worst. Therefore, the modified pathological N category was reasonable solution to of apply TDs into the pN category of TNM staging system.

Legal entity responsible for the study: Fudan University Shanghai Cancer Center

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Disclosure: All authors have declared no conflicts of interest.

496P Predictive potential of tumour-stroma ratio on benefit from adjuvant bevacizumab in high-risk stage II and stage III colon cancer

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Background: The tumour-stroma ratio (TSR) has proven to be an independent prognostic factor in colon cancer.

We evaluated the predictive potential of TSR on disease free survival (DFS) and overall survival (OS) in patients with high-risk stage II and stage III colon cancer who received standard oxaliplatin-based chemotherapy with or without bevacizumab.

Methods: Haematoxylin and Eosin stained tumour slides of 1212 patients (42% of intention-to-treat(ITT)) enrolled in the AVANT trial were microscopically scored for TSR and categorized as stroma-low or stroma-high.

TSR scores were correlated to the primary endpoint DFS and secondary endpoint OS.

Results: Of 1212 tumour slides, 1163 could be scored for TSR. Patients with stroma-high tumours ($n = 339$) had a significant shorter DFS ($p < 0.001$) compared to patients with stroma-low tumours ($n = 824$). In the AVANT trial addition of bevacizumab did not prolong DFS and data suggested a potential detrimental effect on OS.

In our study, the bevacizumab – FOLFOX-4 arm had a significantly shorter DFS compared to FOLFOX-4 in stroma-low tumours, with a hazard ratio (HR) of 1.94 (95% CI 1.24 – 3.04; $p = 0.004$). However, in stroma-high tumours the effect was reversed and showed a trend for better DFS when adding bevacizumab to FOLFOX-4 versus FOLFOX-4 (HR 0.61 (95% CI 0.35 – 1.07; $p = 0.08$)). For bevacizumab- XELOX versus FOLFOX-4, this was not seen (stroma-low HR 1.07 (95% CI 0.64-1.77; $p = 0.80$); stroma-high HR 0.78 (95% CI 0.47-1.30; $p = 0.35$)). For OS the same pattern was observed for bevacizumab – FOLFOX-4 versus FOLFOX-4 with a HR of 2.53 (95% CI 1.36-4.71; $p = 0.003$) for stroma-low and HR 0.50 (95% CI 0.22-1.14; $p = 0.10$) for stroma-high tumours. For bevacizumab – XELOX versus FOLFOX-4, this was 1.13 (95% CI 0.55-2.31; $p = 0.74$) for stroma-low tumours and HR 0.74 (95% CI 0.37-1.51; $p = 0.41$) for stroma-high tumours.

Conclusions: Addition of bevacizumab to intravenous oxaliplatin-based chemotherapy suggests, in accordance with AVANT ITT analysis, a pronounced shorter DFS and OS in low stromal tumours. In contrast, in high stromal tumours a (potential) beneficial trend is observed when adding bevacizumab to intravenous oxaliplatin-based chemotherapy.

Clinical trial identification: NCT00112918

Legal entity responsible for the study: Hoffmann-La Roche

Funding: None

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497P Tumor-stroma interactions and response to targeted agents in preclinical models of colorectal cancer (CRC)

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Background: Recent evidence suggests that genetically "normal" tumor microenvironment may react to pathway inhibitors by upregulating signaling pathways and modulating the sensitivity of cancer cells to targeted agents. The aim of this study was to uncover the mechanisms by which stromal cells modulate the sensitivity of tumor cells in response to signaling inhibitors.

Methods: We monitored the functional effects of MEK and PI3K/mTOR inhibitors (trametinib/gedatolisib) on isogenic CRC cell lines (HCT116 and HCT116 PTEN$^{-/-}$) in the presence or absence of stromal fibroblasts or fibroblast/endothelial cell conditioned medium (CM); moreover, we evaluated pathway activation under different culture conditions and analysed the cytokine/chemokine profile.

Results: Trametinib/gedatolisib combinations were additive in HCT116 (combination index, CI = 1) and strongly synergistic in HCT116 PTEN$^{-/-}$ (CI = 0.25). Under conditions of direct cell-cell contact, co-culture with HCT116 PTEN$^{-/-}$ rendered fibroblasts hypersensitive to combined trametinib/gedatolisib combinations, while co-culture with HCT116 actually protected the stromal component. CM from different types of stromal cells (fibroblasts: HFF, HF, BJ; endothelial cells: EA.hy926) differentially affected the response of HCT116 (but not HCT116 PTEN$^{-/-}$) to signalling inhibitors: in particular, HFF- and EA.hy926-CM rendered HCT116 hypersensitive to PI3K/mTOR blockade by single-agent gedatolisib moreover, EA.hy926 rendered HCT116 PTEN$^{-/-}$ more sensitive to trametinib. Pathway activation analysis showed more prominent downregulation of AKT phosphorylation in response to PI3K/mTOR inhibition in the presence of fibroblast-conditioned medium. Angiogenesis microarrays demonstrated a diversified profile of cytokine/chemokine production in stromal cells from different sources, particularly in terms of IL-6, IL-8 and MCP-1 production.

Conclusions: Stromal cells differentially affected response of CRC to agents targeting the MAPK and PI3K pathways; such effects varied depending on the genetic background of the tumor cell (PTEN-competent or PTEN-loss) and on the modality of tumor stroma interaction (direct cell contact or soluble factors).

Legal entity responsible for the study: IFO- Regina Elena National Cancer Institute

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Disclosure: All authors have declared no conflicts of interest.

498P Molecular profiling of colorectal tumors stratified by the histological tumor-stroma ratio

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Background: The tumor microenvironment or tumor stroma is a dominant determinant of cancer cell behaviour and disease progression. The presence of high tumor stroma content is likely associated with cancer cells acquiring pro-metastatic capacities. The tumor-stroma ratio (TSR) is a robust prognostic tool that is scored on haematoxylin and eosin (H&E) paraffin sections at the invasive margin of the tumor. The importance of the tumor stroma was also emphasized in the colorectal cancer consensus molecular subtypes (CMS). The CMS classification described four CRC subtypes, of which the poor-prognosis CMS4 subtype is characterized by high stromal infiltration and mesenchymal gene expression. However, the biological mechanism of the tumor stroma is not well understood. We therefore aim to investigate the overall transcriptomic profiles and activated pathways of tumors classified by the TSR method using gene expression data.

Methods: Seventy-one patients with stage I-III colorectal cancer were included in the study with available gene expression data and H&E sections. Firstly, we scored the TSR on H&E sections and performed survival analysis. Secondly, we quantified the amount of stromal cells present in the tumor bulk of the gene expression analysis.Thirdly, we investigated the biological pathways differently activated between the two groups using online currated gene sets of the MSigDB. Finally, we compared the association between the TSR classification and the CMS classification assessed based on gene expression data.

Results: The TSR was an excellent prognostic marker in a multivariable analysis [OS p = 0,0001, HR = 4,59 (1,96 – 10,75)]. Tumors stratified as stroma-high based on histological TSR had significantly more stromal cells compared to stroma-low tumors (p = 2,58*10-5). Pathways related to epithelial-mesenchymal-transition, angiogenesis, extracellular matrix and integrin were significantly different in the two tumor-stroma groups. We found that the TSR and the CMS classification were associated (χ^2 test = 7,71; p = 0,005).

Conclusions: At the moment, we are validating our findings in a second cohort and further investigating genes present the relevant pathways. These results will be presented on the day of the symposium.

Legal entity responsible for the study: Wilma Mesker, assistant professor LUMC

Funding: None

Disclosure: All authors have declared no conflicts of interest.

499P The characteristics and prognostic factors in colorectal cancer containing signet ring cell

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Background: Colorectal signet ring cell carcinoma (SRCC) is a rare entity with poor prognosis. The aim of the study was to investigate the clinicopathological characteristics and identify the prognostic factors in colorectal cancer containing signet ring cell (CRC-SRC).

Methods: We retrospectively analyzed 98 CRC-SRC patients confirmed by pathology from February 1987 to December 2015 in our institute. Age, gender, clinical characteristics, laboratory findings, pathologic grade and TNM staging were studied to identify prognostic factors associated with the overall survival (OS) and progression-free survival (PFS). Statistical analysis was conducted by SPSS 20.0.

Results: Of the 98 patients in this study, 60 rectal patients accounted for 61.2%. Ninety-five (96.9%) patients were diagnosed as stage III or IV tumors, 76 (77.5%) patients had lymph node metastasis, and 27 (27.5%) patients had distant metastasis. The median survival time was 22.1 months (range, 1-165 months). The 1-, 3-, and 5-year OS rates of the patients were 74.5% (95%CI: 65.9%-83.1%), 44.8% (95%CI: 34.8%-54.8%), and 31.2% (95%CI: 21.4%-41.0%), respectively. Preoperative carcinoembryonic antigen (CEA), N staging, M staging, local relapse were associated with OS (χ^2=4.163, 8.320, 11.199, 15.436, P < 0.05), while tumor nodules, postoperative chemotherapy, and postoperative radiotherapy had significant influence on PFS (χ^2=10.039, 11.733, 7.116, P < 0.05). On multivariate analyses, preoperative CEA (HR = 2.514, 95%CI: 1.108-5.704) and distant metastases (HR = 2.127, 95%CI: 0.999-4.525) were independent predictors for survival. Based on the point of 30% and 80%, which was calculated by X-tile, we found that the proportion of signet ring cells in colorectal cancer had no significant influence on OS and PFS.

Conclusions: Long-term follow-up of colorectal SRCC showed that it was a rare subtype of colorectal cancer with poor outcomes. Furthermore, the dismal prognosis was related to the presence of signet ring cells, rather than the proportion of signet ring cells. Preoperative CEA and distant metastases were hopeful to predict prognosis of CRC-SRC independently.

Legal entity responsible for the study: Xiang Quan Kong

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Disclosure: All authors have declared no conflicts of interest.

500P Effect of lateral lymph node dissection for lower rectal cancer: An ad hoc analysis of the ACTS-RC randomized clinical trial

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Background: The phase III ACTS-RC (Adjuvant Chemotherapy for Stage II/III Rectal Cancer) trial showed benefits in relapse-free survival (RFS) in rectal cancer with tegafur, 5-chloro-2,4-dihydropyrimidine, and potassium oxonate (S-1) adjuvant chemotherapy in comparison with uracil and tegafur (UFT) therapy. Lateral lymph node dissection (LLND) has been one of the standard treatments for lower rectal cancer patients in Japan. However, it has been debated whether LLND has survival benefits. The aim of this study was to evaluate the impact of lateral LLND on the outcomes in the ACTS-RC randomized clinical trial.

Methods: In a total of 445 lower rectal cancer cases (Stage I/II/IIIA/IIIB/IIIC: 1/130/10/59/165/80) from 959 rectal cancer cases in the ACTS-RC trial, 215 underwent LLND and 230 did not. UFT and S-1 therapy was prescribed for 110 and 105 patients with LLND, respectively, and for 111 and 119 patients without LLND, respectively.

Results: There were no significant differences in patient background characteristics, except for age and pathological T stage, between the LLND and without-LLND groups. Younger patients were often selected as candidates for LLND, and LLND had no impact on RFS or overall survival (OS) in all patients with lower rectal cancer (hazard ratio [HR]=0.941, 95% confidence interval [CI]: 0.696–1.271). In Stage IIIB/C patients, LLND improved the RFS (HR = 0.762, 95% CI: 0.533–1.091). This trend was the same in both the S-1 (HR = 0.766, 95% CI: 0.449–1.306) and UFT arms (HR = 0.790, 95% CI: 0.487–1.283), despite the better RFS in the S-1 arm than in the UFT arm. LLND did not show a major impact on OS in Stage IIIB/C patients.

Conclusions: This exploratory analysis showed that LLND improves RFS in patients receiving either UFT or S-1 therapy, although the results were not significant. LLND has an additional impact on improving RFS of patients with lower rectal cancer undergoing adjuvant chemotherapy.

Clinical trial identification: UMIN-CTR (C000000385)

Legal entity responsible for the study: Japanese foudation for multidiscipilinary treatment of cancer

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502P Effects of mesorectal fascia (MRF) status for locally advanced rectal cancer: Results of a multicenter, randomized, controlled, phase II trial (FDRT-002)

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Background: To identity the effects of high-dose intensity modulated radiation therapy(IMRT) for locally advanced rectal cancer according to MRF status.

Methods: Eligible patients from multicenter who had histologically confirmed locally advanced rectal adenocarcinoma (cT3-T4 and/or cN+) located within 12 cm from the anal verge, were randomly assigned (1:1) to either the low intensity group (50 Gy/25Fxs concurrent with oxaliplatin 50 mg/m2 weekly and capecitabine 625 mg/m2 bid d1-5 weekly) or the high intensity group (50 Gy/25Fxs and a concomitant boost of 5 Gy to the primary tumor, followed by one cycle of XELOX two weeks after the completion of chemoradiotherapy). Surgery was scheduled eight weeks after the completion of CRT. All patients were recommended to receive postoperative XELOX chemotherapy regardless of pathological stage. The primary endpoint was pathological complete response rate (pCR). Secondary endpoints included LC, OS, DFS and toxicities.

Results: From February 2010 to December 2011, 120 locally advanced rectal cancer patients (60 in high intensity group and 60 in low intensity group) were involved. The data were analyzed by MRF status (74 in the MRF- group and 46 in the MRF+ group). Patients in the MRF- group had better pCR (21.6% vs. 13.0%, p = 0.238), LC (p = 0.012), DFS (p = 0.002) and OS (p = 0.007) than those in MRF+ group. While stratified with MRF status, high intensity group showed a better tumor response, especially in positive MRF group. But no significant interaction between MRF and intensity was found in long-term prognosis.

Conclusions: MRF is a strong prognostic factor and a predictor of tumor regression. High-dose treatment may be beneficial to MRF+ patients via improving tumor response.

Clinical trial identification: NCT01064999

Legal entity responsible for the study: Department of Radiation Oncology, Fudan University Shanghai Cancer Center

Funding: None

Disclosure: All authors have declared no conflicts of interest.

503P Planned organ preservation for selected T2, T3 rectal cancer: French experience using chemo radiotherapy and contact X ray boost

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Background: Combining CRT (50 Gy+ capecitabine) and CXB boost provides high probability of organ preservation. We report the experience of three French institutions using CXB.

Methods: Selection used digital rectal examination, colonoscopy, MRI (and/or Endorectal-ultrasound, 18FDG Pet-CT). Inclusion was: adenocarcinoma (distal, middle rectum), T2 T3a-b, tumor diameter ≤ 4cm, N0, M0. Treatment: CXB (80-110 Gy/3-4 fr) followed by CRT (CAP 50). Tumor response assessed on week 14 after start of treatment using DRE, rigid rectoscopy and MRI. Clinical complete response (cCR) was defined as no visible tumor, supple rectal wall and TRG 1-2 MRI. In case of cCR a close surveillance or local excision was proposed.

Results: Between 2002 -2016, 84 patients were treated (Lyonvilleurbanne: 16, Mâcon: 11, Nice: 57). Median age: 75 years, Male: 59, Female: 25. T2:52; T3:32. Operable patients: 69 (83%). Median follow-up time was 53 months. A cCR was achieved in 94% of cases. Local excision was performed in 16 patients (ypT0/pT1: 14). At 4 years, the cancer specific survival was 82% [CI:96-70] and the local relapse rate 12% [CI: 2-22]. 7 local relapses were seen with 2 after 5 years with one isolated perirectal lymph node relapse at 7 years. Acute grade 3 toxicity (diarrhea, proctitis) was seen in 9 patients mainly related to CRT and did not require treatment modification. Main late toxicity (> 6 months after treatment) was rectal bleeding (due to radiation telangiectasia) which required plasma argon coagulation in 5 patients. No TME surgery was performed and organ preservation was achieved in all cases (75 patients with local control). Bowel function was good (LARS score<20) in 85% of patients with no diverting stoma for poor function.

Conclusions: After adequate selection and treatment, rectal cancer T2T3a-b N0 ≤4cm can achieve a high rate of cCR (≥85%) with organ preservation, good bowel function and low rate of local relapse (< 15%) with low toxicity. Prolonged follow-up is mandatory. As rectal adenocarcinoma is radioresistant tumor, the treatment must combine CRT and CXB boost. Like anal squamous cell cancer, planned organ preservation can be proposed to operable patients. The ongoing European OPERA trial aims at bringing evidence to this option.

Clinical trial identification: OPERA Protocol number: 2014-A01851-46

Legal entity responsible for the study: Centre Antoine Lacassagne, Nice, France

Funding: None

Disclosure: J-P. Gérard: Medical advisor of Ariane Medical system company Derbi, UK All other authors have declared no conflicts of interest.

504P Comparison between magnetic resonance imaging (MRI) and pathology in the assessment of tumour regression grade (TRG) in rectal cancer (RC)

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Background: Based on the ability to distinguish between areas of residual cancer and treatment induced fibrosis after neoadjuvant treatment, a 5-tier MRI-based (mr)TRG system that follows the principles of the pathological (p)TRG system previously proposed by Dworak has been developed for RC. However, limited data exist regarding the correlation between mrTRG and pTRG, and the prognostic value of mrTRG in patients who are assessable for pTRG is unclear.

Methods: mrTRG, as assessed by a radiologist according to Patel et al (J Clin Oncol 2011), and pTRG, as assessed by a pathologist according to Dworak et al (Int J Colorect Dis 1997), were compared in MRI-defined, high-risk, locally-advanced RC patients from two phase II trials (EXPERT and EXPERT-C). All patients had received an intensified neoadjuvant treatment with induction chemotherapy followed by chemoradiotherapy. The agreement between radiologist and pathologist was assessed with the weighted κ test while the Kaplan-Meier method was used to estimate survival outcomes.

Results: 191 patients who had undergone neoadjuvant treatment and surgery with a curative intent were included. Median time from completion of neoadjuvant treatment to pre-operative MRI and surgery was 4.1 weeks (interquartile range [IQR]: 3.7-4.7) and 6.6 weeks (IQR: 5.9-7.6), respectively. Fair agreement was found between mrTRG and pTRG when regression was classified according to standard 5-tier systems ($\kappa = 0.24$) or modified 3-tier systems ($\kappa = 0.25$). After a median follow-up of 65.5 months (95% CI: 65.1-66.2), survival outcomes of patients with intermediate pathological regression (pTRG 2) were numerically better if good/complete regression was also observed on imaging (mrTRG 1-2) compared to poor regression (mrTRG 3-5) (5-year recurrence-free survival 76.9% versus 65.9%, p = 0.18; 5-year overall survival 80.6% versus 68.8%, p = 0.22).

Conclusions: Only fair agreement was found between mrTRG and pTRG which suggests that these parameters may represent biologically distinct phenomena. Assessing tumour regression on pre-operative MRI may provide complementary prognostic information to pTRG and help to refine stratification of RC patients after surgery.

Legal entity responsible for the study: The Royal Marsden NHS Foundation Trust

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505P FOLFIRINOX as induction treatment in rectal cancer patients with synchronous metastases (RCSM): Final results of the FFCD 1102 phase II trial

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Background: Optimal therapeutic strategy in patients (pts) with RCSM remains discussed and many front-line options can be discussed to best treat primary tumor and metastatic disease: surgery (S), radiotherapy (RT), chemoradiotherapy (CRT) or chemotherapy (CT). The FFCD 1102 trial evaluated the efficacy of upfront FOLFIRINOX in this setting.

Methods: Chemotherapy-naïve pts with RCSM received FOLFIRINOX: oxaliplatin 85 mg/m^2 d1 + irinotecan 180 mg/m^2 D1 + leucovorin 400 mg/m^2 d1 followed by 5FU 400 mg/m^2 bolus d1 and 2,400 mg/m^2 46h continuous infusion biweekly; 8 cycles were mandatory. CT-scan and MRI at baseline, 2 and 4 months (m) were centrally reviewed. The objective responses were assessed on CT-scan for metastases (RECIST criteria) and MRI for rectal tumor (volume decrease $\geq$ 70%). The primary endpoint was disease control rate at 4 m (4m DC). With a Simon 2-stage design, a targeted (H1) 4m DC $>$ 75% was defined (unilateral alpha of 5% and statistical power of 90%).

Results: 65 pts were enrolled (07/2012 to 02/2015): male 78%; median age 61 years; PS 0-1 99%; liver metastases 92%; ^{3}2 metastatic sites 63%. All pts received at least 1 cycle of CT, and 85% the 8 planned cycles. The 4m DC was 94% (95% CI, 86.3-97.8). Percentages of patients with local symptoms (rectal bleeding, rectal syndrome, sub-occlusion) were 72%, 16% and 10% at baseline, 2 and 4 m, respectively. For evaluable pts at 4 m, response rates of metastases and primary tumor were 86% (55/64) and 62.5% (30/48). Median follow-up was 35.0 m (95% CI, 31.3-43.7). After 8 cycles of FOLFIRINOX, therapeutic strategy was investigators' choice: 60 pts (92%) received CT, 38 (58%) had a RT or CRT, 32 (49%) a rectal tumor resection (RS), and 22 (34%) a surgery and/or ablation of their metastases (MS). On ITT, median PFS and OS were 10.9 m (95% CI, 8.8-12.9) and 33.4 m (95% CI, 22.6-38.2), respectively. OS were 17.6 m (95% CI, 11.8-26.4) in 28 pts (43%) who had no surgery, 38.8 m (95% CI, 13.6-44.6) in 15 pts (23%) who had RS only, and 42.1 m [33.45-NA] in 22 pts who had MS.

Conclusions: Front-line FOLFIRINOX allows a good local and distant control of RCSM, and leaves the opportunity to decide best therapeutic strategy according to the response obtained after the induction step.

Legal entity responsible for the study: FFCD (Fédération Francophone de Cancérologie Digestive)

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506P Neoadjuvant treatment with mFOLFOXIRI alone versus chemoradiotherapy in locally advanced rectal cancer: A propensity score analysis from two prospective trials

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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, neoadjuvant chemotherapy regimens were under investigation. Here, we aimed to compare the efficacy of preoperative chemotherapy with mFOLFOXIRI alone versus chemoradiotherapy 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 standard CRT or mFOLFOXIRI chemotherapy alone preoperatively were selected for this study. 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 CRT).

Results: A total of 142 patients were included in the study, with median age of 51 years old. After propensity score matching, 71 patients were comparable in the two groups. Comparable pathologic complete response (pCR) rate (15.5% vs. 12.7%, P = 0.63) and tumor downstaging rate (42.3% vs. 36.6%, P = 0.49) were observed in the mFOLFOXIRI group and CRT group, respectively. The anal preservation rate was similar between the two groups (87.3% vs. 88.7%, p = 0.79). But lower incidence of anastomotic fistula (7.0% vs. 19.7%, P = 0.026) was shown in mFOLFOXIRI alone group than that of CRT group. And radiation-related dermatitis or proctitis was occurred in 41.7% of patients in the CRT group.

Conclusions: Preoperative mFOLFOXIRI alone showed similar early efficacy in terms of pCR rate and tumor downstaging rate when comparing with CRT, and led to less toxicity and fewer postoperative complications. But this finding requires further analysis from long-term survival data. The phase III study comparing FOLFOXIRI with CRT is ongoing.

Clinical trial identification: This study included two prospective clinical trials NCT01211210 (FOWARC study) and NCT02217020 (FORTUNE study).

Legal entity responsible for the study: Yanhong Deng

Funding: None

Disclosure: All authors have declared no conflicts of interest.

507P Updated survival results of FACT trial: Multicenter phase II trial of neoadjuvant chemotherapy with mFOLFOX6 for stage II/III rectal cancer with a T3/T4 tumor

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Background: The multicenter phase II FACT trial demonstrated that modified FOLFOX6 (mFOLFOX6) was efficacious treatment for stage II/III rectal cancer patients with a T3/T4 tumor (Koike J, et al. Cancer Chemother Pharmacol 2017). We now reported the disease-free survival (DFS) and overall suravival (OS) after a median follow-up of more than 3 years.

Methods: Patients received four 2-week cycles of mFOLFOX6 therapy (oxaliplatin at 85 mg/m^2 + l-leucovorin at 200 mg/m^2 + fluorouracil as a 400 mg/m^2 bolus followed by infusion of 2,400 mg/m^2 over 46 hours, all on Day 1). They were evaluated by

computed tomography after completion of the fourth cycle. If there was no disease progression, two additional cycles were administered and then surgery was performed. Adjuvant chemotherapy was generally administered for 6 months using various regimens at the discretion of the physician.

Results: At a median follow-up of 42.8 months, median DFS from registration of clinical trials was 42.2 months, and median DFS from surgery was 38.9 months. Median survival time (MST) from registration of clinical trials was 42.8 months, and OS from surgery was 38.9 months. The safety profile was almost similar to previous analysis results.

Conclusions: Neoadjuvant chemotherapy using mFOLFOX6 for stage II/III rectal cancer patients with a T3/T4 tumor was well tolerated, as previously reported. In this trial, neoadjuvant mFOLFOX6 showed improved median DFS and MST.

Legal entity responsible for the study: FACT trial group

Funding: None

Disclosure: All authors have declared no conflicts of interest.

508P Phase II randomized trial of capecitabine + radiation therapy with/without bevacizumab as preoperative treatment for patients with resectable locally advanced rectal adenocarcinoma: Final results of 3 and 5-year disease free survival, distant relapse free survival and overall survival

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Background: Combined modality treatment with preoperative radiation therapy (RT) + capecitabine is a standard of care for locally advanced rectal adenocarcinoma. However, new strategies to improve outcomes are necessary. We previously reported neither differences in pathologic complete response (primary objective) nor in safety results with preoperative RT + capecitabine with or without Bev. We present now the Disease-free survival (DFS), distant relapse free survival (RFS) and Overall Survival (OS) data at 3 and 5 years.

Methods: Patients (pts) were randomized in a 1:1 ratio to 5 weeks (w) of RT 45 Gy with concurrent capecitabine 825 mg/m2 bid x 5 d/w with Bevacizumab (Bev) 5 mg/kg q2w (3 doses) (arm A) or without Bev (arm B). Adjuvant systemic chemotherapy administration was upon investigatoŕs criteria.

Results: Ninety pts were included (44 in arm A and 46 in arm B). Preoperative treatment compliance was similar in both arms. Seventy-five pts received adjuvant systemic chemotherapy: 34 (77.3%) in arm A and 41 (89.1%) in arm B ($p = 0.1313$). One pt (arm B) developed local relapse. Eleven pts in arm A and 10 in arm B developed distant metastasis. With a median follow-up of 63.5 and 63.5 months for arms A and B, respectively, median DFS, median RFS and median OS have not been reached for both arms. DFS at 3 y and 5 y was 75.0% and 68.2% (arm A) vs 71.7% and 69.6% (arm B), respectively (5-y DFS, $p = 0.9820$). Distant RFS at 3 y and 5 y was 81.0% and 76.2% (arm A) vs 80.4% and 78.3% (arm B), respectively (5y-distant RFS, $p = 0.6923$). OS was 88.6% and 81.0% (arm A) vs 95.7% and 87.0% (arm B) at 3 and 5y, respectively (5-y OS, $p = 0.3350$). Five pts had a second malignancy (1 in arm A, 4 in arm B), without significant differences between arms.

Conclusions: In our study, the addition of bevacizumab to capecitabine and radiotherapy in the neoadjuvant setting for locally advanced rectal cancer does not confer benefits in DFS, RFS or OS.

Clinical trial identification: NCT0104384

Legal entity responsible for the study: The Spanish Cooperative Group for the Treatment of Digestive Tumors (TTD)

Funding: Roche

Disclosure: All authors have declared no conflicts of interest.

509P Immunological features of resected tumor after neoadjuvant chemotherapy (NAC) and chemoradiotherapy (CRT) become the superior prediction markers for recurrence in rectal cancer

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Background: Although CRT is the standard neoadjuvant therapy for local advanced rectal cancer (RC), benefits of NAC have also been reported recently. In this study, we investigate whether the tumor microenvironment is related to local therapeutic effects and recurrence free survival (RFS) after neoadjuvant therapy, and explore the role of the anti-tumor immune response in cancer treatment.

Methods: 200 RC patients were enrolled and categorized into three groups according to pretreatment: CRT (n = 48, 5-Fluorouracil or Capecitabine + Radiation), NAC (n = 51, FOLFOX), Surgery alone (n = 101). The infiltration and status of immune cells were assessed by multiplex fluorescence immunohistochemically analysis.

Results: The growth of residual tumor cells after treatment was evaluated using Ki67 expression. Compared with the surgery group, CRT, but not NAC, significantly decreased the percentage of Ki67high cells in cytokeratin positive cells. However, the percentage of Ki67high tumor cells is comparable between all tumor regression grade (TRG) groups. Assessing the immunological features of tumor tissues, we found that the infiltration of T cells into tumors is significantly higher in TRG 1 patients than in patients with TRG 2, 3, and those treated with surgery alone. The percentage of tumor infiltration in Ki67high population of CD4 and CD8 T cells is more prominent, suggesting that aggressive infiltration of T cells might be involved in the treatment effect of neoadjuvant therapies. Notably, in the NAC group, patients with high accumulation of Ki67high CD8 T cells in tumor and stroma tissue experienced long term RFS, compared with patients with low accumulation of Ki67high CD8 T cells. On the other hand, after neoadjuvant therapy with CRT, patients with high accumulation of both CD8 and Ki67high CD4 T cells in tumor achieved long term RFS.

Conclusions: Our results suggested that CRT and NAC had different effects on the tumor microenvironment. The densities of Ki67high CD8 T cells in tumors could be a strong inhibitor of recurrence for RC after NAC. In the case of CRT, the densities of CD8 T cells and Ki67high CD4 T cells in tumors could inhibit recurrence.

Legal entity responsible for the study: National Cancer Center Hospital East

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Disclosure: All authors have declared no conflicts of interest.

510P The ADC value of post-RT might predict TRG after neoadjuvant radiotherapy for local advanced rectal cancer

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Background: This study evaluates the ADC value of post-RT associated with Tumor regression grade (TRG) after neoadjuvant radiotherapy for locally advanced rectal cancer.

Methods: We retrospectively analyzed 88 patients with locally advanced rectal cancer between April 2010 to September 2015. Forty-four patients underwent neoadjuvant short-course radiotherapy, and the other 44 patients underwent neoadjuvant long-course chemo-radiotherapy. The ADC value of post-RT were measured by Diffusion-weighted MRI technology. The slides of surgical specimens were reviewed and classified according to Mandard TRG. We compared patients with good response (Mandard TRG1 + 2) and patients with bad response (Mandard TRG3 + 4+5). The relationship between ADC value of post-RT and TRG was analysised.

Results: In univariate analysis, age ($P = 0.006$), adjuvant chemotherapy ($P = 0.023$), pathological type ($P = 0.024$), differentiation degree ($P = 0.001$), distance from tumor to the anal margin ($P = 0.031$) and TRG ($P = 0.007$) were significantly associated with overall survival(OS). Multivariate analysis showed that TRG ($P = 0.034$) were independently prognostic of OS. There was no significant difference in OS between the long-course chemo-radiotherapy group and short-course radiotherapy group ($P = 0.261$). The 5-year OS between TRG1 + 2 and TRG3 + 4+5 was significant (90.9% vs 67.4%, $P = 0.004$). Neoadjuvant radiotherapy ($P = 0.000$), pT ($P = 0.010$), gross type ($P = 0.020$) and the ADC value of post-RT ($P = 0.002$) were significantly associated with TRG. The best critical point of ADC value of post-RT was $1.71 \times 10^{-3}mm^2/s$ by using ROC curve in predicting TRG1 + 2. The patients with low CEA level before radiotherapy had higher ADC value of post-RT ($ADC \geq 1.71 \times 10^{-3}mm^2/s$), and the difference was statistically significant ($P = 0.024$).

Conclusions: There was no significant difference in OS between long-course chemo-radiotherapy and short-course radiotherapy group. TRG can predict the efficacy of neoadjuvant long-course or short-course radiotherapy in patients with locally advanced rectal cancer. The ADC value of post-RT might predict TRG after neoadjuvant radiotherapy for patients with locally advanced rectal cancer.

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Disclosure: All authors have declared no conflicts of interest.

511P Polyethylene glycol embolics loaded with irinotecan for chemoembolization of refractory liver metastases from colorectal cancer

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Background: Patients with liver metastases from colorectal cancer are in 80% of cases non-indicated for resection. The standard first line treatment of unresectablelivermetastases is systemic chemotherapy, however this method results in progression for 70% of patients. The indicated therapy for refractory patients is the chemoembolization. In this study we monitored tumor response, and adverse events after chemoembolization of colorectal cancer liver metastases with polyethylene glycol embolics loaded with irinotecan. Secondary objectives were to monitor quality of life, time to progression and survival of patients.

Methods: Patients were included in the study if: affected by CRC-LM, who were refractory to systemic chemotherapy, treated with chemoembolization using polythylene glycol embolics, and liver involvement >50%. Tumor response, performance status (PS), tumor marker antigens, and quality of life (QoL) were monitored at 1, 3 and 6 months after chemoembolization. Q oL was assessed with the palliative scale (PSS).

Results: We treated 50 consecutive CRC-LM patients with chemoembolization using polythylene glycol embolics, their tumor response one month after chemoembolization was 28% of complete response (CR), and 48% of partial response (PR), 8% stable disease (SD), and 16% of progression. Tumor response 3 months after chemoembolization was CR 24%, PR 38%, SD 19% and progression disease (PD) 19%. Tumor response 6 months after chemoembolization was CR 18%, PR 44%, SD 21% and progression disease (PD) 18%. QoL was 90% PPS at each time point. Median time to progression was 2,5 months (range 0,8 - 6). Median follow-up was 14 months (0,8-25 range). Chemoembolizations were performed with no complications. Observed side effects (mild or moderate intensity) were: pain in 32% of patients, increase of transaminase levels in 20% fever in 14%, whereas 30% of patients did not complain any adverse event.

Conclusions: Chemoembolization of refractory liver metastases from colorectal cancer with polyethylene glycol embolics loaded with irinotecan was effective in tumor response and resulted in mild toxicity, and good QoL.

Clinical trial identification: NCT01891552

Legal entity responsible for the study: Giammaria Fiorentini

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Disclosure: All authors have declared no conflicts of interest.

512P Neoadjuvant systemic chemotherapy prior to cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for the treatment of peritoneal carcinomatosis from colorectal cancer

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Background: Cytoreductive surgery (CRS) and Hyperthermic Intraperitoneal Chemotherapy (HIPEC) have become a standard treatment option for peritoneal carcinomatosis (PC) arising from colorectal carcinoma, despite the complexity and morbidity of this procedure. The timing of CRS+HIPEC in the course of the disease in unclear, and there is no consensus regarding pre-operative treatments. In this study we analyzed the effect of neoadjuvant systemic chemotherapy prior to CRS+HIPEC on patients' outcome.

Methods: Data on consecutive colorectal patients with PC, treated in the Sourasky Medical Center from Jan 2007 to Dec 2016 was collected. Demographic, pathologic and clinical data was registered for all patients. For patients treated with neoadjuvant chemotherapy, the regimen, duration and responses were recorded. Outcome measurements were postoperative complications, progression free survival (PFS) and overall survival (OS).

Results: Seventy-two (72) patients were identified, of whom 43 (59.7%) were treated with neoadjuvant chemotherapy and 29 (40.3%) were referred directly to CRS+HIPEC. No significant demographic, pathological or clinical differences between the groups were found. Median PFS was 12 months in the Neo- group and 17 months in the Neo+ group ($p = 0.015$). On multivariate Cox-PH analysis, the effect of neoadjuvant chemotherapy on PFS was maintained ($HR = 0.34$, $p = 0.002$). Median OS was 41 months in the Neo- and 47 months in the Neo+ with no statistical difference. In the Neo+ group, on univariate analysis, there was no significant effect to chemotherapy regimen, duration of treatment, nor best response. There was no difference in postoperative complication rate between the groups.

Conclusions: In patients candidate for CRS+HIPEC for the treatment of PC from colorectal cancer, the administration of systemic neoadjuvant chemotherapy significantly prolongs PFS with no additional postoperative risks. Prospective randomized trials and larger patient cohorts are needed to confirm these findings and assess the effect on OS.

Legal entity responsible for the study: Tel Aviv University

Funding: None

Disclosure: R. Geva: Advisory board member: Bayer, MSD, Novartis. Honoraria: BMS, Lilly, Medison, Roche, Novartis, Janssen: Travel expenses: Roche, BMS All other authors have declared no conflicts of interest.

513P Efficacy and tolerability of chronomodulated FOLFIRINOX (chronoIFLO) as 1st or 2nd line treatment in patients (pts) with metastatic colorectal cancer (MCC): Final results from an international trial (EORTC 05011)

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Background: FOLFIRINOX is an effective yet toxic protocol against gastro-intestinal cancers. We report final updated global results from a randomised international trial aiming to identify the least toxic time of Irinotecan (I) combined with Oxaliplatin (O), 5-Fluorouracil (F) and Leucovorin (L).

Methods: 199 MCC pts were randomised to receive chronomodulated I (180 mg/m2 over 6-h) on day 1 (d1) with peak delivery at 1:00, 5:00, 9:00, 13:00, 16:00 or 21:00, followed by 4-d fixed-time chronomodulated O (20 mg/m2/d) over 11.5 h, with peak delivery at 16:00, alternating with F (700 mg/m2/d) and L (300 mg/m2/d) over 11.5 h, with peak delivery at 4:00. ChronoIFLO was administered every 3rd week using an automatic programmable-in-time pump.

Results: 136 males (68%) and 63 females (32%) were registered at 18 centers. They had a median age of 61 years (range: 30-81), a WHO PS of 0 (73%), 1 (23%) or 2 (4%). ChronoIFLO4 was given as 1st (154 pts, 77%) or 2nd line (45 pts, 23%; 14 pts had previously received I and 20 pts, O). Pt features were similar in the 6 treatment groups. Median number of cycles was 6 (1-18), and mean relative dose intensities were 88% for I, 88% for O, 89% for F. Overall grade 3-4 toxicity occurred in 136/199 pts (68%) and 248/1158 cycles (21%). The most common severe toxicities were diarrhoea (43% of pts), nausea (19%), neutropenia (17%), fatigue (13%) and anorexia (11%). 1st line chronoIFLO achieved an objective response rate (ORR) of 61% [95% Confidence Limits: 53-69], a disease control rate (DCR) of 90% [85-95], a median progression-free survival (PFS) of 8.7 months (mo) [7.6-9.8], and a median overall survival (OS) of 19.5 mo [14.8-24.2]. Respective figures for 2nd line were: ORR, 39% [24-54]; DCR, 76% [63-89]; PFS, 7.4 mo [5.4-9.3]; OS, 16.6 mo [12.5-20.7].

Conclusions: Chronomodulated triplet showed favourable safety and activity profiles both as frontline or salvage treatment of MCC, in comparison to previous reports of conventional delivery. The therapeutic index of chronoIFLO could benefit from the personalisation of drug delivery patterns to match individual differences in internal clock phase.

Clinical trial identification: EORTC 05011

Legal entity responsible for the study: Warwick Medical School

Funding: Warwick Medical School

Disclosure: All authors have declared no conflicts of interest.

514P A multicentre, randomized phase 3 study on the optimization of the combination of bevacizumab with mFOLFOX/OXXEL in patients with metastatic colorectal cancer (mCRC)

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Background: Bevacizumab is a humanized anti-vascular endothelial growth factor (VEGF) monoclonal antibody, approved in combination with chemotherapy in the treatment of mCRC. It is proposed that the schedule of administration might be critical

and that anticipating bevacizumab to chemotherapy, might improve treatment efficacy.

Methods: mCRC patients, ≤ 75 years old, ECOG PS ≤ 1, having received no more than one previous treatment, with at least one measurable lesion according to RECIST, were randomized (1:1) to receive standard administration of bevacizumab (5mg/kg d1 Q14) with chemotherapy (mFOLFOX/OXXEL regimen for 12 cycles) vs experimental bevacizumab given 4 days before chemotherapy (same dose), at each cycle. Patients could receive maintenance bevacizumab (7.5 mg/kg d1 Q21) until disease progression or unacceptable toxicity in both arms. Primary end point was the objective response rate (ORR). With 80% power and 2-tailed alpha 0.05, an expected 20% increase in response rate, 230 patients were planned. With 163 events, the study also had 80% power to detect a hazard ratio (HR) 0.64 of progression-free survival. Analyses were based on intention to treat.

Results: From May 2012 to Dec 2015, 230 patients were randomly assigned to experimental (n = 115) and standard (n = 115) arm. Median age was 62 (IQ range 53-68), 79% were PS 0, 93% were not pretreated, 53% had a single metastatic site, 54% were RAS-mutant (47% and 62% in the standard and experimental arm, respectively). ORR was 54% in both arms (p = 0.89). With a median follow-up of 32.4 months, 204 PFS events and 131 deaths were reported. Median PFS was 10.5 and 11.7 months (HR 0.79, 95% CI: 0.60-1.05; multivariate adjusted p = 0.10) and median OS was 23.7 and 29.9 months (HR 0.73, 95% CI: 0.52-1.04; multivariate adjusted p = 0.08), in the standard and experimental arm, respectively. 57.4% and 59.1% of the patient received a following treatment in the standard and experimental arm, respectively.

Conclusions: Anticipating bevacizumab to chemotherapy does not improve ORR. A not statistically significant prolongation of PFS and OS was reported in this study. Supported by the Italian Ministry of Health. CT.gov NCT01718873.

Clinical trial identification: EudraCT Number: 2011-004997-27

Legal entity responsible for the study: Istituto Nazionale Tumori, IRCCS, Fondazione G. Pascale

Funding: Italian Ministry of Health

Disclosure: A. Avallone: Travel, accommodation: Roche and Amgen; honoraria for consulting: Bayer, Roche and Amgen. F. Perrone: Travel, accommodation: Roche, Lilly, Bayer, Daiichi Sankyo; honoraria: Amgen, Novartis, Lilly, Roche, Bayer, Daiichi Sankyo; research funding to institution: Roche and Bayer. M.C. Piccirillo: Travel, accommodation: Roche and Bayer; honoraria for consulting: Bayer. All other authors have declared no conflicts of interest.

515P First-in-human Phase I study of bacterial RNA interference therapeutic CEQ508 in patients with familial adenomatous polyposis (FAP)

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Background: FAP is an inherited gastrointestinal (GI) disorder that predisposes patients to early-onset of colorectal cancer due a mutation in the APC gene resulting in nuclear accumulation of β-catenin. CEQ508 is a live-attenuated Escherichia coli genetically engineered to produce and deliver β-catenin short-hairpin RNA into the mucosa. This first-in-human study (START-FAP) aimed to assess the safety, tolerability, and efficacy in response to CEQ508 in FAP patients.

Methods: Six patients with FAP were orally administered (3 each in Cohort 1 and 2) with CEQ-508 (10^8 and 10^9 CFU/day for 28 days). The primary objective was to establish safety profile of oral CEQ508 and to determine the MTD. The secondary objective was the extent of knockdown of the target gene β-catenin in GI tissues (duodenum, ileum, right and left colon, antrum) taken during endoscopy at baseline and at end-of-treatment (EOT). β-catenin expression levels were measured using qPCR and normalized to housekeeping genes (EIF2B1, HPRT1, GUSβ). A mixed-model nested-ANOVA was used to evaluate β-catenin knockdown.

Results: Daily oral dosing of 10^8 and 10^9 CFU of CEQ508 for 28 days was well-tolerated. Histology of polyps and normal mucosa at baseline and EOT indicated no changes in tissue morphology or inflammation in cohort 1 patients. A slight inflammation (from score of 0 to 1 at EOT) was noted in normal colon mucosa of cohort 2 patients. Daily oral dosing of 10^9 CFU of CEQ508 for 28 days was well-tolerated with targeted β-catenin knockdown in polyps. β-catenin expression was highest in duodenum and lowest in antrum with no significant treatment effects in normal mucosa. Significant reduction was observed in overall β-catenin expression in polyps at EOT (P = 0.0005). Reduction was observed primarily in the duodenum (39.3%, P < 0.0001) and ileum (28.8%, P = 0.012).

Conclusions: Bacterial delivery of RNAi in FAP patients demonstrated an acceptable safety profile at the two dose levels tested. Without hitting MTD, START-FAP achieved both the primary endpoint of safety and secondary endpoint of b-catenin knockdown. CEQ508 is now being moved into clinical development in combination with Celecoxib/Lisinopril (IT-102) against FAP.

Legal entity responsible for the study: Marina Biotech

Funding: None

Disclosure: V. Trieu, L. Hwang: Officers and own stocks for Marina Biotech. All other authors have declared no conflicts of interest

516P A Multicentre Phase I/II Study of TAS-102 with nintedanib in patients with metastatic colorectal cancer refractory to standard therapies (N-task force: EPOC1410)

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Background: TAS-102 demonstrated significant improvement in overall survival (OS) over placebo in patients (pts) with metastatic colorectal cancer (mCRC). Nintedanib is a triple angiokinase inhibitor of VEGFR (1, 2, 3), PDGFR (a, β), and FGFR (1, 2, 3). In preclinical models, the combination of TAS-102 plus nintedanib demonstrated enhanced activity against CRC compared with either drug alone. This study was conducted to determine the recommended phase II dose (RP2D) and evaluate the efficacy and safety in pts with mCRC refractory to standard therapies. RP2D was determined nintedanib 200mg BID every day adding to standard-dose of TAS-102 in the phase I part (Nishina T, et al. ESMO 2016). We present here on the efficacy and safety data from the ongoing study.

Methods: The key eligibility criteria were pts with mCRC refractory or intolerant to fluoropyrimidine, irinotecan, oxaliplatin, anti-angiogenesis inhibitor and anti-EGFR antibody (if wild-type RAS) and without prior regorafenib. Primary endpoint was investigator-assessed progression-free survival (PFS) rate at 16 weeks in pts treated with RP2D. Using a single stage binomial design, this study required 52 pts, with the PFS rate at 16 weeks of 40% deemed promising and 25% unacceptable (alpha=0.1; beta=0.2).

Results: From August 2015 to August 2016, 55 pts were enrolled. Among them, 52 pts received the RP2D as full analysis set. The PFS rate at 16 weeks was 38.5% (80% confidence interval: 29.3–48.3%). Four pts (7.7%) achieved a partial response, median PFS and disease control rate were 3.7 months and 69.2%, respectively. Median OS was 9.2 months. The median number of treatment cycles was 4 (range 1 - 14). The most common grade 3 or worse treatment-associated adverse events were neutropenia (59.6%), anemia (17.3%), thrombocytopenia (11.5%) and increased liver enzymes (AST: 9.6%, ALT: 7.7%; asymptomatic reversible elevation without any bilirubin elevation). Febrile neutropenia occurred in two (3.8%) pts. There was no treatment-related death.

Conclusions: Standard-dose of TAS-102 with nintedanib 200 mg BID showed promising antitumor activity with acceptable toxicity for mCRC pts.

Clinical trial identification: UMIN000017114.

Legal entity responsible for the study: Exploratory Oncology Research & Clinical Trial Center

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Disclosure: K. Yamazaki: Honoraria: Bayer Yakuhin, Bristol-Myers Squibb Japan, Chugai Pharma, Daiichi Sankyo, Lilly Japan, Merck Serono, Takeda, Taiho Pharmaceutical, and Yakult Honsha; research funding: Bristol-Myers-Squibb Japan and Sanofi. Y. Kuboki: Corporate-sponsored research: Takeda; Other Substantive Relationships (Taiho Pharmaceutical, Bayer: (Honoraria)) E. Shinozaki: Other Substantive Relationships (Taiho, Merck Serono, Takeda, Ono, Chugai, Yakult, Bayer (Honoraria)) H. Hara: Advisory Board Ono, Chugai Corporate-sponsored-research AstraZeneca, Chugai, Merck Serono, MSD, Ono, Taiho, Takeda, Boehringer Ingelheim, Dainippon Sumitomo, Daiichi Sankyo, Lilly Other Chugai, Taiho, Merck Serono, Yakult Honsha, Lilly(Honoraria) Y. Komatsu: Corporate-sponsored-research (Taiho Chugai Pharma Novartis MSD Ono Pharmaceutical Bayer Yakult Lilly) Other Substantive Relationships (Novartis, Pfizer, Bayer(Honoraria)) (Taiho Chugai Lilly Novartis Merck Pfizer, Bayer (Speaker bureau)) K. Yamaguchi: Corporate-sponsored-research (Taiho MSD daiichi-sankyo Ono Merck Bristol Dainipponn-sumitomo Beringer Yakurut Honsha) Other Substantive Relationships (Taiho Takeda Chugai Merck Yakurut-Honsha Lilly(Speaker bureau)) M. Asayama: Corporate-sponsored research (Takeda) T. Tsushima: Other Substantive Relationships (Chugai Pharmaceutical, Takeda Pharmaceutical, Ono Pharmaceutical, Taiho Pharmaceutical(Honoraria)) S. Nomura: Other Substantive Relationships Asahi-Kasei pharma (immediately family member; employment) A. Sato: Corporate-sponsored-research (Taiho Dainippon Sumitomo Pharma Novartis Ono Pharmaceutical Boehringer Ingelheim Bayer) T. Doi: Advisory Board(Lilly, Chugai, Kyowa Hakko Kirin, Novartis, MSD, Daiichi Sankyo, Amgen) Corporate-sponsored-research (Taiho, Merck, Astellas, Janssen, Takeda, Pfizer, Lilly, Sumitomo Group, Bayer, Chugai, Kyowa Hakko Kirin, Boehringer, Novartis, MSD, Daiichi Sankyo, Celgene) A. Ohtsu: Corporate-sponsored-research BMS Other Substantive Relationships Celgene (immediately family member; employment) T. Yoshino: Corporate-sponsored-research

GlaxoSmithKline K.K.Boehringer Ingelheim GmbH All other authors have declared no conflicts of interest.

517P BEACON CRC: safety lead-in (SLI) for the combination of binimetinib (BINI), encorafenib (ENCO), and cetuximab (CTX) in patients (pts) with BRAF-V600E metastatic colorectal cancer (mCRC)

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Background: Phase 2 data for the combination of ENCO (a selective BRAF inhibitor) + CTX (an anti-EGFR antibody) in pts with $BRAF^{V600E}$ mCRC showed the regimen was well tolerated and improved response rate, progression-free survival, and overall survival compared with historical controls. BEACON CRC (NCT02928224) is a randomized phase 3 study evaluating both the triplet combination BINI (a MEK inhibitor) + ENCO + CTX and the doublet combination ENCO + CTX compared with investigators' choice of irinotecan (IRI) + CTX or FOLFIRI (folinic acid, 5-fluorouracil, and IRI) + CTX in pts with $BRAF^{V600E}$ mCRC whose disease has progressed after 1 or 2 prior regimens in the metastatic setting. Here we describe the results of the SLI to determine the safety of the triplet combination.

Methods: Nine pts with $BRAF^{V600E}$ mCRC would receive ENCO 300 mg QD + BINI 45 mg BID + CTX 400 mg/m^2 (then 250 mg/m^2 QW) in 28-day cycles. If < 33% of pts had a dose-limiting toxicity (DLT), 16–21 additional pts would be treated at the same dose. If ≥ 33% of pts had a DLT, lower doses of BINI and/or ENCO would be assessed.

Results: Thirty pts received the initial dose level; median age was 59 years, 17 pts were female, and 17 had an ECOG PS of 0. DLTs were reported in 5 pts: infusion reaction following CTX (n = 2), inability to receive ≥75% dose intensity due to grade 2 retinopathy (n = 2), and grade 2 decreased ejection fraction (n = 1). The most common adverse events (% of pts with grade 1, 2, 3, 4) were diarrhea (38, 28, 3, 0), nausea (41, 3, 0, 0), dermatitis acneiform (38, 7, 0, 0), and fatigue (21, 14, 7, 0). Twenty-eight pts continue on treatment; 1 pt died due to rapid disease progression and 1 pt discontinued due to disease-related biliary obstruction. Preliminary efficacy data support the benefit of adding BINI to the doublet regimen; additional follow-up will provide mature safety and efficacy data from the SLI cohort and will be presented.

Conclusions: ENCO + BINI + CTX, at the full planned dose of each agent, was generally well tolerated. Safety and preliminary efficacy data support the initiation of the phase 3 portion of the BEACON trial.

Clinical trial identification: NCT02928224

Legal entity responsible for the study: Array BioPharma Inc.

Funding: Array BioPharma Inc.

Disclosure: E. Van Cutsem: Consulting: Bayer, Boehringer Ingelheim, Lilly, Novartis, Merck Serono. Research funding: Amgen, Bayer, Boehringer Ingelheim, Celgene, Ipsen, Merck, Novartis, Roche, Sanofi. M. Fakih: Advisory board: Array BioPharma. C. Montagut: Consulting: Merck, Amgen, Symphogen, Sanofi. J. Desai: Honoraria: Novartis, Amgen, GlaxoSmithKline. Consulting: Plexxikon, Bionomics, Roche, Novartis, Lilly. Research Funding: Novartis, Roche, GlaxoSmithKline. T. Yoshino: Research Funding: GlaxoSmithKline K.K., Boehringer Ingelheim GmbH. F. Ciardiello: Advisory Board: Roche, Merck, BMS, Lilly, Amgen, Bayer. H. Wasan: Advisory Board/ Speaker Bureau: Merck Serono, Pfizer, Array BioPharma Inc. K. Maharry, A. Gollerkeri: Employment: Array BioPharma Inc. S. Kopetz: Compensation from: Amgen, Merrimack, Bayer, Array BioPharma, Genentech, MolecularMatch, Symphogen, EMD Serono, Merck. All other authors have declared no conflicts of interest.

518P Sequential therapy with bevacizumab and epidermal growth factor receptor-directed agents for metastatic colorectal carcinoma: A retrospective, registry-based analysis

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Background: Although bevacizumab and monoclonal antibodies directed against epidermal growth factor receptor (EGFR) cetuximab and panitumumab are commonly used in the treatment of metastatic colorectal cancer (mCRC) without activating RAS mutations, the optimal sequencing of these agents is currently unclear.

Methods: A national registry of targeted therapies was used to analyse baseline characteristics and outcomes of patients with mCRC who received bevacizumab followed by antiEGFR agents or a reverse sequence as first- and second-line treatment. The cohort for analysis included all patients with valid data in the registry who met the following inclusion criteria: a) sequential therapy with first-line cetuximab or panitumumab and second-line bevacizumab or first-line bevacizumab and second-line cetuximab or panitumumab; b) progression documented in the database between the first and the second line; c) first-line therapy using FOLFOX or FOLFIRI regimens as chemotherapy backbone; and d) wild-type KRAS status and wild-type or unknown NRAS status.

Results: The cohort included 490 patients; 181 patients received cetuximab or panitumumab as a part of first-line treatment and bevacizumab as a part of second-line treatment, while 309 patients were treated with the reverse sequence. Median overall survival (OS) from the initiation of first-line therapy was similar for patients treated with the different sequences (Table). No statistically significant differences in OS were detected between patients treated with the different sequences for subgroups of patients defined by age, chemotherapy backbone, synchronous/metachronous metastatic disease, anatomic location of the primary tumour, RAS status, and body-mass index. Progression-free survival, calculated as the time from the initiation of first-line therapy to progression on the second-line therapy moderately favoured the bevacizumab → antiEGFR sequence (Table).

Conclusions: This retrospective analysis of data from a large patient registry does not support the hypothesis that the sequence of antiEGFR agents and bevacizumab has an impact on OS of mCRC patients.

Legal entity responsible for the study: Tomas Buchler

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Table: 518P

	antiEGFR →bevacizumab (n = 181)	bevacizumab →antiEGFR (n = 309)	log-rank p
OS (months)	31.8 (95% CI 27.5–36.1)	31.4 (95% CI 27.8–35.0)	0.940
Progression-free survival (months)	19.3 (95% CI 17.3–21.3)	21.1 (95% CI 19.3–23.0)	0.016

519P Outcomes in patients receiving maintenance therapy in two panitumumab (Pmab) first-line trials for metastatic colorectal cancer (mCRC)

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Background: Maintenance therapy for mCRC is intended to prolong progression-free survival (PFS) with reduced toxicity, but little information is available concerning the value of epidermal growth factor receptor-targeted antibodies in this setting. Here we present data on outcomes of maintenance therapy from two first-line Pmab trials.

Methods: These retrospective analyses include data from patients with RAS WT (no mutations in KRAS or NRAS exons 2, 3 and 4) mCRC from two randomised trials: PRIME (Pmab + FOLFOX vs. FOLFOX) and PEAK (FOLFOX + either Pmab or bevacizumab). Maintenance therapy was defined as continuation of the other components of the patient's study treatment after discontinuation of oxaliplatin. PFS and overall survival (OS) from baseline and from start of maintenance therapy were summarised for patients without progression in each treatment arm.

Results: In PRIME and PEAK, 93 and 61 patients with RAS WT mCRC, respectively, received maintenance therapy (median [IQR] duration: PRIME, 16 [7–37] months; PEAK, 20 [13–41] months). Median PFS and OS overall and from start of maintenance therapy were longer in patients receiving Pmab maintenance vs. controls in both studies (Table).

Conclusions: Even if time to oxaliplatin discontinuation is heterogeneous and patients receiving maintenance treatment are among those with greater treatment benefit, these retrospective data suggest that deintensification of Pmab-based treatment to 5-fluorouracil/Pmab maintenance is feasible and associated with extended PFS and OS. While maintenance is not part of the licensed indication for Pmab, physicians may drop oxaliplatin in patients with good initial response, to minimize toxicity, with the hypothesis that outcome would not be impacted. Ongoing prospective trials should confirm the value of Pmab maintenance and inform the design of future trials in which treatment strategy and sequence will be studied.

Clinical trial identification: PRIME: NCT00364013 PEAK: NCT00819780

Legal entity responsible for the study: Amgen

Funding: Amgen

Disclosure: F. Rivera Herrero: Advisory boards and/or received research funding from Amgen, Bayer, Celgene, Lilly, Merck Serono, MSD, Roche, Servier, and Sanofi. J-B. Bachet: Advisory boards and received research funding from Amgen, Bayer, Celgene, Merck Serono, Sanofi, and Servier. D.P. Modest: Honoraria and participated in advisory boards for Amgen, Bayer, Merck, MSD, Roche, Servier, and SIRTEX; travel support/research funding from Amgen, Bayer, Merck, Roche, and Servier. F. de Braud: Advisory boards and consultancy roles for Amgen, Eli Lilly, Merck Serono, Roche, and Servier. F. Pietrantonio: Advisory boards and consultancy roles for Amgen, Bayer, Eli-Lilly, Roche, and Sanofi. R. Koukakis: Employee of Amgen Ltd and owns restricted shares in Amgen. G. Demonty: Employee of Amgen (Europe) GmbH and owns restricted shares in Amgen. J-Y. Douillard: Steering committee involvement for Amgen and Bayer; advisory boards, symposia and consultancy for Amgen, Merck Serono, Roche, Sirtex and Takeda; advisory boards for Boehringer Ingelheim and Sanofi; and research funding from Merck Serono.

520P AMALTHEA: A prospective, single-arm study of the Hellenic Cooperative Oncology Group evaluating the efficacy and safety of 1st line FOLFIRI+Aflibercept in patients with metastatic colorectal cancer

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Background: The efficacy and safety of the FOLFIRI regimen combined with aflibercept has not been studied in the first-line management of patients with metastatic colorectal cancer (mCRC).

Methods: In the context of a prospective single-arm trial, patients with mCRC received standard doses of Leucovorin, 5-Fluorouracil and Irinotecan (FOLFIRI) combined with aflibercept (4 mg/KBW iv) every 2 weeks until disease progression, unacceptable toxicity or completion of 12 cycles, followed by aflibercept maintenance. Endpoints were the 12-month Progression-Free Rate (PFR12), efficacy and toxicity.

Results: 73 fit patients were enrolled in the study between 2014 and 2016. Fifty-five patients had tumors in the left colon, forty-four presented with synchronous metastases. Median relative dose intensities administered were 0.85 (95% CI 0.74-0.84) for 5-FU CI, 0.80 (95% CI 0.73-0.89) for Irinotecan and 1.0 (95% CI 0.92-0.98) for Aflibercept. In total, adverse events occurred in 70 patients (95.9%), with no toxic deaths. The most common grade 3 or 4 adverse events were neutropenia (13 patients, 18%), febrile neutropenia (3 patients, 4%), diarrhoea (11 patients, 15%), hypertension (19 pts, 26%), proteinuria (8 pts, 11%), infections (8 pts, 11%), mucositis (6 pts, 8%). Among 85 adverse events of special interest (AESI) observed, 57 events ended with complete recovery. Among eight patients with severe proteinuria, improvement to grade 0/2 occurred in six at a median time of 4.8 months. The Objective Response Rate (ORR) was 46.6% in the ITT population (n = 73) and 51.5% in the evaluable population (n = 66). Among potential prognostic clinicopathological parameters (including RAS, BRAF status, primary site), the presence of synchronous metastases and a relapse-free interval <12 months were significantly associated with response (odds ratio 2.92 and 3.75 respectively), while a performance status of 0 with overall survival (hazard ratio 0.42). At a median follow-up of 20.9 months, the median OS was 24.7 months (95% CI 17.3-30.5), the median PFS 8.4 months (95% CI 7.44-9.44), while the 12-month PFS rate was 21.8%.

Conclusions: The FOLFIRI + Aflibercept regimen is active and safe, however it failed to improve historical benchmarks of efficacy in chemonaive patients with mCRC.

Clinical trial identification: EudraCT No.: 2013-002567-26

Legal entity responsible for the study: Hellenic Cooperative Oncology Group (HeCOG)

Funding: Sanofi-Aventis

Disclosure: V. Karavasilis: Advisory Board: Novartis, Roche, Astellas, Merck, Sanofi, Pfizer, Astra-Zeneca, Janssen. Honoraria: Novartis, Roche, Astellas, Merck, Sanofi, Pfizer, Astra-Zeneca, Janssen. G. Aravantinos: Honoraria: Genesis pharma SA Scientific Advisory Board: Amgen, Astra-Zeneca, BMS, GSK, Roche, Sanofi. I. Souglakos: Honoraria: Sanofi. Research grant: Sanofi. G. Fountzilas: Honoraria: Astra-Zeneca. Consulting or Advisory Role: Pfizer, Sanofi, Roche. Stock and other ownership interests (an Immediate family member): Ariad. All other authors have declared no conflicts of interest.

Table: 519P

	PRIME		PEAK	
	Pmab + 5-FU maintenance (n = 52)	5-FU maintenance (n = 41)	Pmab + 5-FU maintenance (n = 31)	Bev + 5-FU maintenance (n = 30)
Survival from baseline, months (95% CI)				
PFS	16.6 (11.3–23.6)	12.6 (9.4–16.2)	15.4 (11.6–18.4)	13.1 (9.5–16.6)
OS	40.2 (30.3–50.4)	24.1 (17.7–33.0)	39.1 (34.2–63.0)	28.9 (21.0–32.0)
Survival from start of maintenance, months (95% CI)				
PFS	11.7 (7.8–19.2)	7.1 (5.6–10.2)	9.7 (5.8–14.8)	7.0 (3.9–10.6)
OS	33.9 (24.7–42.8)	16.4 (12.4–24.1)	33.5 (24.5–54.9)	23.3 (15.7–26.3)
Oxaliplatin cycles before maintenance therapy, median (range)	12 (2–31)	13 (5–41)	11 (3–21)	12 (3–19)
Restarted oxaliplatin during maintenance, n (%)	13 (25)	2 (5)	5 (16)	5 (17)

5-FU, 5-fluorouracil; Bev, bevacizumab; CI, confidence interval; OS, overall survival; PFS, progression-free survival; Pmab, panitumumab

521P Multicenter phase II study of biweekly XELIRI plus bevacizumab as a second-line therapy in patients with metastatic colorectal cancer (JSWOG-C3 study)

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Background: Triweekly capecitabine plus irinotecan (XELIRI) is not completely regarded as a valid substitute for fluorouracil, leucovorin, and irinotecan (FOLFIRI) in metastatic colorectal cancer (mCRC) because of the potential for greater toxicity. Therefore, we conducted a phase II study to assess the efficacy and safety of biweekly XELIRI plus bevacizumab (BV) as second-line chemotherapy for mCRC. High dose BV (10 mg/kg) combined biweekly XELIRI as second-line chemotherapy was one of the first trial in the world.

Methods: Patients with mCRC who had received prior chemotherapy including oxaliplatin based regimen were eligible for this study. Protocol treatment administrated capecitabine 1,000 mg/m2 twice daily from the evening of day 1 to the morning of day 8, intravenous irinotecan 150mg/m2 on day 1, and BV 10 mg/kg on day 1 every 2 weeks. The primary endpoint of this study were progression-free survival (PFS) and safety. The secondary endpoint were overall survival (OS), time to treatment failure (TTF), response rate (RR) and disease control rate (DCR).

Results: Between January 2013 and July 2015, 51 patients were enrolled in this study. The patients' characteristics were as follows: median age, 66 years (range 41–82); male/female, 29/22; The median PFS was 5.7 months (95% confidence interval, 4.2–7.2 months). The median OS was 13.4 months (95%CI, 11.4–16.7 months). The median TTF was 5.2 months (95%CI, 3.9–7.2 months). The response rate was 14%, and the disease control rate was 78%. Grade 3 or higher adverse events were mainly febrile neutropenia in two patients and hypertension in 14 patients (28.6%). One patient had grade 4 intestinal pneumonia but improved by intensive treatment. There were no other severe adverse events or treatment-related deaths.

Conclusions: In mCRC patients, biweekly XELIRI + BV 10 mg/kg is effective and feasible as second-line chemotherapy. Biweekly XELIRI + BV is considered a useful substitute for FOLFIRI + BV in mCRC, and further study of this combination therapy is warranted.

Legal entity responsible for the study: Japan Southwest Oncology Group

Funding: Japan Southwest Oncology Group

Disclosure: All authors have declared no conflicts of interest.

522P Sex-related differences in circadian-dependent tolerance of Irinotecan (I) added to chronomodulated (chrono) 5-Fluorouracil (F), Leucovorin (L) and Oxaliplatin (O): Final results from international randomised time-finding study in patients with metastatic colorectal cancer (MCC)

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Background: The least toxic time (LTT) of I varied by up to 8 hours according to sex in mice (Li et al. Cancer Res 2013). The translational relevance was investigated through a post-hoc analysis of a randomised trial, where the planned methodology did not identify the LTT of I combined with F, L and O (chronoIFLO) in the whole population.

Methods: 199 MCC patients at 18 EU centers were randomised to receive chrono I (180 mg/m2 over 6-h, with peak delivery at 1:00, 5:00, 9:00, 13:00, 17:00 or 21:00) on day (d) 1, followed by fixed-time chrono O (20 mg/m2/d over 11.5 h; peak delivery at 16:00) and F-L (700 and 300 mg/m2/d, respectively, over 11.5h, with peak delivery at 4:00), for 4 d. ChronoIFLO was administered q3 weeks as 1st or 2nd line. The main endpoints were the circadian profiles of Grade (G) 3-4 toxicity and best objective response (OR), according to sex. Rhythmic trends were determined with cosinor using smoothed data through moving average.

Results: The trial included 136 males (m; 68%) and 63 females (f; 32%), with similar characteristics among the 6 treatment groups. The rates of all G3-4 toxicities ranged from 64% to 69.6% in m, and from 50% to 93.3% in f according to I timing. The LTT was at 12:30 [95% CI, 11:30-13:30] in m ($p = 0.002$), and at 15:55 [12:40-19:08] in f ($p = 0.05$) for all G3-4 toxicities. G3-4 neutropenia varied >3-fold as a function of I timing (10 to 33.3% in m; 0 to 38.5% in f), and the least corresponded to I peak delivery at 11:00 [08:00-13:08] in m ($p = 0.045$) and 18:07 [15:07-21:08] ($p = 0.047$) in f. Similar circadian trends were found for mucosal G3-4 toxicities in both sexes. No timing effect was found for G3-4 diarrhoea. OR rates ranged from 38.9% to 80% in m, and 37.5% to 83.3% in f between groups, with most effective timing of I overlapping with LTT in m (14:50 [11:52-17:26], $p = 0.039$), but not in f (02:17, $p = 0.074$).

Conclusions: Optimal timing of I tolerability occurred 4 to 7 h earlier in m as compared to f, in agreement with prior mouse data. The relevance of sex for the determination of optimal efficacy timing is further supported here.

Clinical trial identification: EORTC 05011

Legal entity responsible for the study: Warwick Medical School

Funding: Warwick Medical School

Disclosure: All authors have declared no conflicts of interest.

523P Mechanism of pelareorep (Pel)-mediated cell death in a Phase I study in combination with irinotecan/fluorouracil/leucovorin/bevacizumab (FOLFIRI/B) in patients with KRAS mutant metastatic colorectal cancer (mCRC)

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Background: Pelareorep (REOLYSIN) is an immuno oncology viral agent that contains a naturally occurring, ubiquitous, non-enveloped human dearing strain reovirus. Pelareorep selectively replicates in tumor cells harboring gene mutations that downregulate the IFN-induced antiviral response (e.g., KRAS-mutations) which results in their lysis. Pel is synergistic with irinotecan (IRI) in in vitro and in vivo models.

Methods: This is a phase I dose escalation study of FOLFIRI/B + Pel. Eligible pts are adults with oxaliplatin refractory KRAS-mutant mCRC. Both, IRI (150-180 mg/m^2) and Pel ($1x10^{10}$ $TCID_{50}$ to $3x10^{10}$ $TCID_{50}$) were escalated. Pel was given IV over 1 hr days 1-5 every 4 weeks (wk). Primary objectives were to determine toxicity, recommended phase two dose (RPTD), and pharmacokinetics. Secondary objectives were response rate, progression-free and overall survival (PFS and OS). Tumor biopsies post Pel were optional and subject to electron microscopy (EM).

Results: 36 pts enrolled; FOLFIRI naïve (24) and pre-treated (12). Common (>10%) grade 3-4 toxicity include: neutropenia, anemia, and thrombocytopenia. At 180 mg/m^2 of IRI, among FOLFIRI pretreated pts, 2 had dose-limiting toxicity (DLT) in cycle 1; in FOLFIRI naïve patients, none/6 had a DLT, with a median PFS of 49 wk (range: 10-91 wk). 5 patients are currently on therapy. The RPTD is IRI 180 mg/m^2 and Pel $3x10^{10}$ $TCID_{50}$. Of 32 evaluable pts, 3 had a partial response. EM of tumor biopsies showed dying cells with degenerating endoplasmic reticulum, large nonfunctional mitochondria, heterochromatin, condensed DNA, and viral factories, both empty and active. There were discrete holes in the cytoplasm leading to dampening of cellular proliferation. Immunogold staining against viral capsid protein σ demonstrated viral "homing" in the tumor cells. Flow cytometry reveals expansion of dendritic cells with consequent activation of cytotoxic T cells.

Conclusions: The combination was safe, well tolerated, with a PFS (49 wk), superior to historic data (25-30 wk). Detailed PK and immune data will be presented.

Clinical trial identification: NCT01274624

Legal entity responsible for the study: Oncolytics Inc.

Funding: Conquer Cancer Foundation

Disclosure: S. Goel: Research Funding from Oncolytics Inc. A. Ocean: Research Funding from Oncolytics Inc. A.A. Gutierrez: Chief Medical Officer of Oncolytics Biotech Inc. Employee of Oncolytics Biotech Inc. (or one of its affiliated corporations) and own shares in or have options to purchase shares in Oncolytics Biotech Inc. M. Coffey: President and CEO of Oncolytics Biotech Inc. Employee of Oncolytics Biotech Inc. (or one of its affiliated corporations) and own shares in or have options to purchase shares in Oncolytics Biotech Inc. G. Gill: Employee of Oncolytics Biotech Inc. (or one of its affiliated corporations) and own shares in or have options to purchase shares in Oncolytics Biotech Inc. All other authors have declared no conflicts of interest.

524P Bevacizumab first line and impact on subsequent anti-EGFR activity

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Background: Authors hypothesize that initial anti-VEGF therapy may induce biological changes that then increase the risk of acquired resistance to subsequent EGFR inhibitors.

Methods: A retrospective cohort study was performed to compare the characteristics and survival of patients who were treated with an anti-EGFR therapy at 2nd line and beyond. We separated two groups defined by the first line therapy; 1. chemotherapy plus bevacizumab (CB) and 2. chemo (C) alone. Two survival times were measured for this in this updated analysis; survival from the time of commencing first line chemotherapy and survival from commencement of anti-EGFR therapy. We analysed outcomes separately for the 2nd line anti-EGFR groups (2L) and the '3rd line and beyond' (3L) groups, Long rank (mantel-cox) test analysis was performed to determine whether receiving first line bev was associated with worse overall survival (OS).

Results: 450 mCRC patients who received either CB (n = 249) or C (n = 201), and then an anti-EGFR therapy were studied. Significant differences between CB and C groups for patient characteristics included; decreased median age (61.3 years (range 20.6 - 86.7) v 64.5 (24.3 - 91.8), p = 0.0006), lower use of irinotecan regimens (22% v 42%) and increased use of single agent FU (11% v 1.5%). There was no difference in gender (males 65.5% v 66.7%). There was no difference in proportion of patients receiving anti-EGFR second line (2L), CB 39% v C 43%. Where BRAF MT status was assessed 11% had MT (CB 23% v C 0). Median OS for the 2L group, as measured from the commencement of first line therapy, was 24.4 months for CB v 18.9 months for C (p = 0.0176). Median OS for the 3L group from the commencement of first line therapy was 32.8 months for CB v 29.9 months for C (p = NS). The survival from commencement of anti-EGFR therapy for CB v C respectively was; 2L 10.5 months v 11.6 months (p=NS), 3L 9.9 months v 8.3 months (p=NS).

Conclusions: Overall survival was significantly improved for CB compared to C when measured from initial treatment. This likely reflects patient selection. Overall survival however from commencement of 2L or 3L anti-EGFR was not altered significantly by prior exposure to bevacizumab in this population based registry.

Legal entity responsible for the study: Adelaide Colorectal Tumor Group

Funding: None

Disclosure: T.J. Price: Advisory board member of Roche, Merck, Amgen. Travel support: Amgen. All other authors have declared no conflicts of interest.

525P Efficacy of anti-EGFR antibodies combined with chemotherapy for elderly patients with RAS wild-type metastatic colorectal cancer: A systematic review and metanalysis

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Background: The incidence of Colorectal Cancer (CRC) increases with age, reaching a peak around 70-75 years. The anti-EGFR monoclonal antibodies combined with chemotherapy represent a valid option in patients with RAS wild-type (wt) metastatic CRC (mCRC), allowing a significant improvement in survival. However, few data are available regarding the use of these agents in the elderly population. The aim of the study is to evaluate the efficacy of adding anti-EGFR monoclonal antibodies (Cetuximab or Panitumumab) to chemotherapy in the treatment of RAS wt mCRC older patients.

Methods: A systematic review of the published data using PubMed and EMBASE databases and the congress documents of the main national and international symposia was performed. The random effect model was used to combine the effect estimates, the I^2 and Cochran's Q index to quantify the between-study heterogeneity unexplained by sampling error.

Results: Four randomized trials (two regarding Cetuximab and two Panitumumab combined with 5-FU based doublet chemotherapy) have been selected among the 2765 initially identified studies. None of the studies had been specifically designed for the elderly population, so PFS and OS HR values were extracted from pre-specified subgroup analyses. In our study, 605 elderly patients were included: 289 patients received only chemotherapy and 316 patients received chemotherapy in combination with anti-EGFR antibodies. The meta-analysis showed a statistically significant benefit of the combination of chemotherapy and anti-EGFR against chemotherapy alone both in terms of PFS (HR 0.79, IC 95% 0.64-0.98, p = 0.028, Q = 2.54, df = 3, I^2 = 0%) and OS (HR 0.82, IC 95% 0.68-0.98, p = 0.032, Q = 0.57, df = 3, I^2 = 0%). The subgroup-analyses confirmed that the Panitumumab studies had a major impact than Cetuximab ones on the final metanalysis result.

Conclusions: The addition of Cetuximab or Panitumumab to chemotherapy could represent a valid therapeutic option in terms of efficacy, also in elderly patients with RAS wt mCRC. However, the available data in this subset of patient are limited. Dedicated studies are needed in order to determine the best therapeutic strategy.

Legal entity responsible for the study: Azienda Ospedaliero-Universitaria di Ferrara

Funding: None

Disclosure: All authors have declared no conflicts of interest.

526P Efficacy of panitumumab and cetuximab in elderly patients (aged ≥75) with chemotherapy-refractory wild-type KRAS exon 2 metastatic colorectal cancer (mCRC): Retrospective analysis of data from nationwide drug-reimbursement-access program

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Background: Panitumumab and cetuximab are standards of treatment for chemotherapy-refractory, wild-type KRAS exon 2 mCRC patients. There are limited data on efficacy of these drugs in elderly patients.

Methods: Data were obtained from 2425 patients enrolled into nationwide Panitumumab/Cetuximab Reimbursement-Access Program ongoing in 62 Polish cancer centres. All reported patients were included to analyses from April 2012 to December 2015. Key inclusion criteria to the program: mCRC, refractory to chemotherapy (5FU, oxaliplatin, irinotecan), aged ≥18 years, wild-type KRAS exon 2 tumour status, measurable disease, ECOG performance status 0-2. Inclusion and exclusion criteria were the same for panitumumab and cetuximab therapy in all centres. Pre-planned, uniform schedule of efficacy assessment (every 12 weeks) was applied from start of therapy in all centres. Individual patients data concerning efficacy outcome measures were entered prospectively via electronic system into databases of public, national payer - National Health Fund (NFZ). We performed retrospective analysis using Kaplan-Meier method to assess overall survival (OS) and progression-free survival (PFS). OS and PFS were compared by log-rank test between patients aged <75 and ≥75.

Results: Out of 2425 patients, 247 were aged ≥75 years (10%) (165 patients received panitumumab and 82 received cetuximab). In panitumumab group, median OS was comparable in younger and older patients, 9.9 vs 9.6 months, respectively (HR, 1.07; 95% CI: 0.87-1.31; p = 0.5121), as was median PFS, 5.5 vs 5.8 months (HR, 1.08; 95% CI: 0.85-1.38; p = 0.5206) (n = 994 vs n = 130). In cetuximab group, median OS was also comparable in younger and older patients, 10.2 vs 9.9 months, respectively (HR, 0.95; 95% CI: 0.73-1.23; p = 0.6749), as was median PFS, 5.2 vs 5.2 months (HR, 0.92; 95% CI: 0.67-1.30; p = 0.6352) (n = 559 vs n = 60).

Conclusions: Panitumumab and Cetuximab provide similar efficacy outcomes in younger and older patients in everyday practice.

Legal entity responsible for the study: Military Institute of Medicine, Warsaw National Health Fund, Poland

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527P Toxicity and efficacy of flat-dosed versus body-surface area (BSA)-dosed capecitabine

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Background: Capecitabine (cape) is a pro-drug for the cytotoxic agent 5-fluorouracil and widely used in the treatment of colorectal cancer. In general, cape is dosed on body surface area (BSA), despite all drawbacks of this dosing strategy. In this study, toxicity and efficacy of flat-dosed cape (i.e. without adjustments for body size) was analysed, and compared to BSA-dosed cape.

Methods: All patients treated with cape at our center between 2003-2015 were included when they had been treated with flat-dosed cape and no prior treatment with fluoropyrimidines. Data on adverse events and survival was collected. Cape-specific toxicity (CS_{tox}) was defined as toxicity grade for diarrhea ≥ 3, hand-foot syndrome ≥ 2 and neutropenia ≥ 2. Clinical relevant toxicity (CR_{tox}) consisted of hospital admission, dose delay, reduction or discontinuation. Patients were divided per treatment in 3 groups based on BSA-quartiles: lowest 25%, middle 50% and highest 25%, corrected for sex. Toxicity was compared using the X^2-test and binary logistic regression analysis. Survival analysis was done by the Kaplan-Meier method.

Results: Among 1952 evaluated patients; 1055 patients were included (60% male). Three regimes were evaluated: cape-radiotherapy (CRT, n = 769), cape-oxaliplatin (CAPOX, n = 189) and cape monotherapy (MONO, n = 97). The mean dose of flat-dosed cape was 7.1% lower compared to BSA-dosed cape (p < 0.01). CS_{tox} and CR_{tox} occurred in 20% and 27% of patients, respectively. The X^2-test per BSA-group showed no difference in CS_{tox} and CR_{tox} in CAPOX and MONO (p > 0.05), for CRT there was

a difference in CS_{tox} ($p = 0.009$) and CR_{tox} ($p = 0.014$). Corrected for sex, age and renal function, only in the CRT group BSA predicted CS_{tox} (OR: 0.248, 95% CI: 0.072-0.857, $p = 0.028$) and CR_{tox} (OR: 0.246, 95% CI: 0.083-0.727, $p = 0.011$). Survival analyses for CAPOX and CRT showed no differences between BSA-groups and median survival was comparable to literature.

Conclusions: Flat-dosed cape is safe in CAPOX and MONO. Only in CRT, BSA is predictive for CS_{tox} and CR_{tox}. No survival differences could be identified in subgroups. Therefore, flat-dosed cape is a safe and effective dosing strategy in regimens without RT.

Legal entity responsible for the study: Department of Medical Oncology, Erasmus MC Cancer Institute

Funding: None

Disclosure: All authors have declared no conflicts of interest.

528P Efficacy of panitumumab and cetuximab in patients with chemotherapy-refractory wild-type KRAS exon 2 metastatic colorectal cancer (mCRC): Retrospective analysis of data from nationwide drug-reimbursement-access program

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Background: Panitumumab and cetuximab are standards of treatment for chemotherapy-refractory, wild-type KRAS exon 2 mCRC patients. There are limited data on efficacy of these drugs in everyday practice on national level.

Methods: Patients enrolled into nationwide Panitumumab/Cetuximab Reimbursement-Access Program ongoing in Polish cancer centres. All reported patients were included to analyses from April 2012 to December 2015. Key inclusion criteria to the program: mCRC, refractory to chemotherapy (5FU, oxaliplatin, irinotecan), wild-type KRAS exon 2 tumour status, measurable disease, ECOG performance status 0-2. Inclusion and exclusion criteria were the same for panitumumab and cetuximab therapy in all centres. Pre-planned, uniform schedule of efficacy assessment (every 12 weeks) was applied from start of therapy in all centres. Individual patients data concerning efficacy outcome measures were entered prospectively via electronic system into databases of public, national payer - National Health Fund (NFZ). We performed retrospective analysis using Kaplan-Meier method to assess overall survival (OS) and progression-free survival (PFS). Objective response rate (ORR) was also reported.

Results: As of April 2012, 2425 patients were enrolled into the program in 62 cancer centres (1527 patients received panitumumab and 898 received cetuximab). Median follow-up was 17.9 months for panitumumab and 25.3 months for cetuximab. Median OS was 9.9 months (95% CI 9.4-10.5) with panitumumab and 10.2 months with cetuximab (95% CI 9.5-10.9). There was no OS significant difference between groups ($p = 0.09$). Median PFS was 5.6 months (95% CI 5.5-5.7) with panitumumab ($n = 1124$) and 5.2 months (95% CI 4.9-5.4) with cetuximab ($n = 619$). There was no PFS difference between groups ($p = 0.16$). ORR was 16% in panitumumab and 13% in cetuximab group.

Conclusions: Panitumumab and Cetuximab provide similar efficacy outcomes in everyday practice in one health care system. Reimbursement, centralized drug-access programs may serve as a source of data for survival analysis on national level.

Legal entity responsible for the study: Military Institute of Medicine, Warsaw National Health Fund, Poland

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529P Multicenter randomized phase II trial (BEVATOMOX) assessing the raltitrexed, oxaliplatin and bevacizumab combination versus FOLFOX6 bevacizumab as 2nd line treatment in metastatic colorectal cancer (mCRC)

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Background: The FOLFOX-Bev combination as 2nd line after Irinotecan-based chemotherapy (CT) failure is efficient in mCRC treatment, independently of the tumour RAS status. The Raltitrexed-Oxaliplatin (TOMOX) combination is reported with acceptable toxicity in mesothelioma patients (pts). Our multicentre randomized phase II study assessed the 6-month progression-free survival (6-PFS) of the TOMOX-Bev combination as 2nd line treatment in mCRC pts.

Methods: Pts OMS≤2 with histologically-proven mCRC, resected/asymptomatic primary tumor, unresectable metastases, and progressive metastatic disease (RECIST) after Irinotecan-based CT, were randomized (1:2) receiving either FOLFOX6 plus Bev (C arm, Bev IV 5mg/kg, then FOLFOX6 D1=D15, 12 cycles) or TOMOX plus Bev (Exp arm, Bev IV 7.5mg/kg, Raltitrexed IV 3mg/m^2 according to creatinine clearance, then Oxaliplatin 130mg/m^2 IV, D1=D21, 8 cycles). Primary endpoint was the 6-PFS. Main secondaries were toxicity, objective response and overall survival (OS). 92 pts, 30 and 62 in the C and Exp arms, were to be recruited.

Results: Due to low accrual rate, 83 pts (63.9% men) were included between 07.2011 and 05.2016, 33 and 50 in the C and Exp arms. Median age was 66 years (48-82). Primary tumour was localized in the left (48.2%) and right colon (37.3%) or rectum (18.1%), resected in 72.3% (36% with adjuvant CT). All pts (RASmt 54.2%) were pretreated with FOLFIRI, combined with anti-EGRF (7%) or Bev (92%). Median numbers of study treatment cycles were 8 and 4 in the C and Exp arms. Major grade 3-4 toxicities (C and Exp arms) were mucositis (12.1 *vs* 12.5%), paresthesia (0 *vs* 6.3%), hand-foot syndroma (3 *vs* 0%) and neutropenia/febrile (6.1/3 *vs* 8.2/2%). The 6-PFS rates were 51.5% (95%CI: 36-67) and 38% (95%CI: 26-51) in the C and Exp arms, and median OS was 11.1 (9.5-16.4) and 9.3 (5.7-11.6) months, respectively. In the Exp arm, OS was longer in pts with left colon tumour *vs* right (11.1 vs 4.6 months).

Conclusions: The TOMOX-Bev combination is feasible as 2nd line treatment in mCRC pts with acceptable toxicity. We cannot conclude in terms of efficacy due to low accrual rate. We confirm a longer OS in pts with left colon tumour.

Clinical trial identification: NCT01532804

Legal entity responsible for the study: ICM Regional Cancer Institute of Montpellier

Funding: Hospira

Disclosure: All authors have declared no conflicts of interest.

530P Safety analysis of phase Ib study of FOLFOXIRI plus ramucirumab as first-line therapy for patients with metastatic colorectal cancer

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Background: Ramucirumab (Rmab), an anti-VEGFR-2 antibody, inhibits VEGF-A, -C, -D binding and endothelial cell proliferation, although bevacizumab (Bmab) binds to and blocks circulating VEGF-A. We conducted a phase Ib study to determine the recommended phase II dose (RP2D) of FOLFOXIRI plus Rmab for metastatic colorectal cancer (mCRC) patients.

Methods: The eligibility criteria included patients with histologically confirmed unresectable colorectal adenocarcinoma, aged 20-75 years, ECOG PS 0-1 (patients > 70 years were eligible if their ECOG PS was 0), wild-type or heterozygous UGT1A1 *28 or *6, no history of prior chemotherapy, and adequate organ function. Three dose levels were planned as follows; oxaliplatin and Rmab dose was fixed at 85 mg/m^2 and 8 mg/kg, respectively. Level 1: 5-fluorouracil (5-FU) 3200 mg/m^2, irinotecan (IRI) 165 mg/m^2, Level 0 as starting dose: 5-FU 2400 mg/m^2, IRI 150 mg/m^2, and Level -1: 5-FU 2400 mg/m^2, IRI 120 mg/m^2. Patients were enrolled with a 3 + 3 design manner to evaluate the dose-limiting toxicity (DLT) in the first cycle.

Results: From September 2016 to February 2017, we enrolled a total of 10 patients (4 patients in the Level 0 and 6 patients in the Level 1). The patients' characteristics were as follows: median age (range), 64 (44-68); male/female, 6/4; ECOG PS 0/1, 8/2; RAS wild/mutant, 1/9; UGT1A1 *1*1/*1*28, 4/6. One patient was excluded for the DLT evaluation due to lack of safety evaluation on cycle 1 day 8. No DLT was observed in the 9 DLT-evaluable patients. In the first cycle, major adverse events were G 4 neutropenia ($n = 2$), G 3 neutropenia ($n = 1$), G 3 hypertension ($n = 1$), G 1/2 diarrhea ($n = 6$), G 1/2 anorexia ($n = 3$), G 2 allergic reaction ($n = 1$), G 1 fatigue ($n = 4$), G 1 peripheral neuropathy ($n = 4$), G 1 nausea ($n = 2$) and G 1 stomatitis ($n = 2$). G-CSF was administered in 2 patients during the first cycle.

Conclusions: The RP2D for FOLFOXIRI plus Rmab was determined at the Level 1. A randomized phase II study of FOLFIRI plus Rmab versus FOLFOXIRI plus Rmab for chemotherapy-naïve mCRC patients (WJOG9216G trial; UMIN000026527) is ongoing. The update results will be presented in the congress.

Clinical trial identification: UMIN000023277

Legal entity responsible for the study: Shizuoka Cancer Center

Funding: Shizuoka Cancer Center

Disclosure: All authors have declared no conflicts of interest.

531P Prognostic factors and specific populations in the pharmacogenetic randomized phase II trial of FOLFIRI with high-dose (HD) of irinotecan vs standard doses in metastatic colorectal cancer (mCRC) patients (pts) according to UGT1A1 genotype

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Background: Pts with a favourable UGT1A1 genotype (homozygous wild type *1/*1 and heterozygous *1/*28) can be treated with HD of irinotecan without significant adverse events. This randomized phase II trial aimed to evaluate the efficacy and safety of FOLFIRI regimen with HD of irinotecan (HD-FOLFIRI) in mCRC pts. Pts genetically at risk for toxicity (*28/*28) were excluded. Potential prognostic factors and specific population subgroups are presented.

Methods: Chemotherapy-naïve patients with the UGT1A1 *1/*1 or *1/*28 genotypes were randomized to receive HD-FOLFIRI vs FOLFIRI every two weeks. Irinotecan doses for UGT1A1 *1/*1 and *1/*28 pts in the experimental group were 300mg/m^2 and 260mg/m^2 respectively. The standard irinotecan dose of 180mg/m^2 was administered in the control group. Main clinical-pathological characteristics and clinical outcomes of pts included were analysed.

Results: Between Jun-12 and Oct-16 82 pts were included. The ORR was significantly higher in the experimental group (67.5% vs 43.6%; p = 0.001). There were not interactions between ORR and clinical characteristics (sex, age, ECOG, tumour location, synchronous disease) and RAS/BRAF status. However, when BRAF mutation was considered, no objective response was observed in the control group compared with 41.7% of pts treated with HD-FOLFIRI (p = 0.003). Metastatic surgical resection was performed in 15 pts (22.5% in HD-FOLFIRI and 15.4% in FOLFIRI) and was associated with ORR (29.5% vs 5.7%; p = 0.007). Median PFS and OS were 8.6 and 26 months (m) (HD-FOLFIRI) and 8.2 and 29 m (FOLFIRI). ECOG 0/1(9.9 vs 7.2 m) and metastatic resection (15.5 vs 7.8 m) were significantly associated with PFS. In terms of OS pts with metastatic surgery (not reach vs 18.4 m) achieved better outcome. Multivariate analysis showed significant association between metastatic resection with both, PFS and OS.

Conclusions: These data confirm the safety of chemotherapy with HD of irinotecan and demonstrate that such strategy improves ORR, which may, in turn, impact favourably on pts survival, especially in those with poor prognosis.

Clinical trial identification: Eudra CT: 2012-000221-42

Legal entity responsible for the study: Institut de Recerca de l'Hospital de la Santa Creu i Sant Pau

Funding: Spanish Ministry of Health and Social Policy - EC11/336

Disclosure: All authors have declared no conflicts of interest.

532P Analysis of efficacy and prognostic factors in second-line chemotherapy for BRAF V600E mutant metastatic colorectal cancer

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Background: *BRAF V600E* mutant (MT) metastatic colorectal cancer (mCRC) has distinct clinicopatholigical features and extremely poor prognosis. First-line chemotherapy was studied in reports assessing cytotoxic doublets or triplets with or without antibodies, but treatment outcomes of second-line chemotherapy were still unknown. The aim of this study is to examine the efficacy of second-line chemotherapy and evaluate prognostic factors in *BRAF V600E* MT patients (pts).

Methods: We retrospectively reviewed *BRAF V600E* MT mCRC pts who underwent second-line chemotherapy between 2007 and 2016. *BRAF* status was examined by PCR-based assay.

Results: Of 71 *BRAF V600E* MT pts, 51 received second-line chemotherapy. Before second-line chemotherapy, baseline patient characteristics were as follows: median age (range), 59 (28–86) years; male/female, 20/31; Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0/1/≥2, 17/28/6; histology low, intermediate/high grade or mucinous status, 34/17; primary tumor location right/left side, 29/22; metastatic site liver/peritoneum, 29/35; metastatic sites 1/≥2, 11/40; and Glasgow Prognostic Scale (GPS) 0/1/2, 23/14/12. As first-line chemotherapy, 48 pts (94%) received oxaliplatin- or irinotecan-based regimens, including 5 (10%) who received FOLFOXIRI. In second-line chemotherapy, 39 pts (76%) received oxaliplatin- or irinotecan-based regimens. Median progression-free survival (PFS) and overall survival (OS) were 2.5 and 6.2 months (M). Overall response and disease control rates were 7% and 43%. All regimens achieving partial responses were BRAF inhibitors in combination with anti-EGFR bodies. Therefore, response rate was 0% if 4 pts treated with trial drugs were excluded. Multivariate analyses for both PFS and OS showed that GPS was an independent prognostic factor. Median OS in pts with GPS 0, 1, and 2 was 10.0, 5.0, and 1.6 M, respectively.

Conclusions: We revealed the dismal results of second-line chemotherapy in *BRAF V600E* MT mCRC pts. GPS can predict the treatment outcomes and identify pts unfit for chemotherapy, indicating that GPS is useful in future clinical trials targeting *BRAF V600E* mutation.

Legal entity responsible for the study: Aichi Prefecture

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533P A large retrospective multicenter study evaluating prognosis and chemosensitivity of metastatic colorectal cancer with microsatellite instability

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Background: Deficient Mismatch Repair (dMMR) and/or microsatellite instability-high colorectal cancers (CRC) represent 12% of all tumors. dMMR non-metastatic CRC are associated with good prognosis but also with resistance to adjuvant 5FU. dMMR metastatic CRC (mCRC) is found in 5% and its influence on prognosis and chemosensitivity is little known.

Methods: This multicenter study included patients with dMMR mCRC treated between 2005 and 2015 in 18 French centers. The Kaplan-Meier method was used to calculate overall survival (OS) and progression-free survival (PFS). Prognostic variables were evaluated in univariate (Log rank test) and multivariate analyses (Cox regression model).

Results: 284 patients with dMMR mCRC were included. Lynch syndrome was found in 43% and *BRAF* mutation in 32%. Median OS was 25.0 months. Peritoneal carcinomatosis (p < 0.01) and surgery of metastasis (p < 0.01) were associated with OS in multivariate analysis but not *BRAF* mutation and Lynch syndrome. 37% of patients had surgery of metastasis, 79% received first-line chemotherapy (palliative or perioperative), 46% second-line, 16% third-line. First-line regimens were 5FU-based (n = 20), oxaliplatin-based (n = 106) or irinotecan-based (n = 82) without or with anti-VEGF (n = 71) or anti-EGFR (n = 34). Median PFS on first-line chemotherapy was 5.7 months and in multivariate analysis only surgery of metastasis was associated with PFS (p < 0.01). Median PFS and OS on palliative first-line chemotherapy (n = 149) were 3.9 months and 17.9 months. Median PFS (3.9, 4.4 and 3.0 months, p = 0.20) and OS (17.9, 16.8 and 23.9 months, p = 0.14) were not different according chemotherapy regimen (5FU-based, oxaliplatin-based and irinotecan-based). The addition of bevacizumab or anti-EGFR therapy were associated with a non-significant increased of PFS as compared to chemotherapy alone (4.6, 6.0 and 3.5 months, p = 0.06). In second-line, median PFS and OS were 3.5 months and 15.8 months. In third-line, median OS was 6.3 months.

Conclusions: This study suggests that dMMR mCRC are associated with poor prognosis with conventional chemotherapy with or without bevacizumab or anti-EGFR. Only surgery of metastasis was associated with better PFS.

Legal entity responsible for the study: Tougeron David

Funding: None

Disclosure: D. Tougeron: Consulting or advisory role for Amgen, Sanofi, Celgene. Travel or accommodation from Ipsen, Amgen, Sanofi. J. Taieb: Honoraria: Amgen, Merck, Roche, Baxalta, Celgene, Sanofi, Lilly, Sirtex. T. André: Honoraria: Roche, Bms, Sanofi. All other authors have declared no conflicts of interest.

534P Exploratory analysis of baseline microsatellite instability (MSI) status in patients with metastatic colorectal cancer (mCRC) treated with regorafenib (REG) or placebo in the phase 3 CORRECT trial

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Background: A high degree of MSI (MSI-H) has been associated with a good prognosis in early-stage CRC. However, emerging evidence suggests that MSI-H patients may have a worse response to chemotherapy in the metastatic setting. Here, we evaluate

survival outcomes by baseline MSI status in patients with mCRC in the CORRECT phase 3 trial.

Methods: CORRECT was an international, multicenter, placebo-controlled trial of 760 patients with treatment-refractory mCRC. Patients were randomized 2:1 to receive oral REG 160 mg or placebo once daily for Weeks 1–3 of each 4-week cycle. Subgroup analysis included patients in the safety population (≥1 dose of study drug) who consented to genetic biomarker studies and from whom archival tissue was available. Next-generation sequencing of archival tumor was performed using the FoundationONE gene panel (Foundation Medicine, Cambridge, MA). Overall survival (OS) and progression-free survival (PFS) by MSI status and its potential interaction with treatment were assessed by a Cox proportional hazards model and Kaplan–Meier analysis.

Results: Archival tumor tissue was available for 229 of the 760 randomized patients (Table). Of the 229 patients, 42 (18%) were MSI-H and 187 (82%) were non-MSI-H, 62% were male, 57%/43% were ECOG performance status 0/1, 58% had a KRAS mutation, and 3% had a BRAF mutation. Although there was less clinical benefit in patients in the MSI-H subgroup, no significant association was detected between MSI status and treatment interaction with OS or PFS in the multivariate analysis (P = 0.15).

Table: 534P

	MSI-H (n = 42)	Non-MSI-H (n = 187)
Regorafenib, n (%)	27 (64)	114 (61)
Placebo, n (%)	15 (36)	73 (39)
Overall survival, HR (95% CI)	0.97 (0.45, 2.07)	0.78 (0.53, 1.15)
Progression-free survival, HR (95% CI)	0.78 (0.39, 1.56)	0.48 (0.35, 0.67)

CI, confidence interval; HR, hazard ratio

Conclusions: This retrospective exploratory analysis of a small subgroup of patients with mCRC from CORRECT shows a prevalence of MSI-H at ~15-20% and no interaction between MSI status and REG treatment benefit. Due to small sample sizes in the subgroups no firm conclusions can be drawn and further studies are necessary to assess the correlation of MSI status with REG clinical benefit.

Clinical trial identification: NCT01103323

Legal entity responsible for the study: Bayer

Funding: Bayer

Disclosure: K. Köchert, G. Beckmann: Employment: Bayer. M. Teufel: Stocks and employment: Bayer.

535P Investigation of MSI status in acquired resistance to 5-fluorouracil treatment in colorectal cancer using a SILAC-based quantitative proteomic analysis method

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Background: Colorectal cancer (CRC) still has a 45% mortality rate, and one of the barriers to therapeutic success is the development of acquired resistance to 5-fluorouracil (5-FU), the most commonly used drug in CRC treatment. Here we establish cell culture models and use state of the art proteomics methods to increase our understanding of how CRC cells develop resistance to 5-FU.

Methods: We develop 5-FU resistant CRC sublines with different microsatellite stability (MSS) profiles, since MSS is a key genetic alteration in CRC formation, and aim to use these to identify new biomarkers of 5-FU response. 5-FU resistant sublines for 2 cell lines, DLD-1 (microsatellite instability phenotype (MSI)) and HT-29 (MSS), were developed by continuous 5-FU exposure, and resistance fold changes of 130.2 and 3.5 respectively were achieved. Once 5-FU resistant sublines were developed they were analysed proteomically using a stable isotope labelling with amino acids in cell culture SILAC-approach and Orbitrap Fusion™ Tribrid™ Mass Spectrometry analysis, to identify new biomarkers of drug resistance.

Results: A total of 3003 proteins were commonly quantified in the parent cell lines (low and high passage numbers), and in the DLD-1 5-FU and HT 29 5-FU resistant sublines. Six proteins were seen to be significantly up-regulated, and eight down-regulated, in both 5-FU resistant sublines when compared to the parent cell lines.

Conclusions: This is the first use of a proteomics approach to study protein expression changes in 5-FU resistant CRC cell lines with varying microsatellite stability status, while accounting for changes which occur in the parent lines over the duration of establishing the resistant sublines. We have identified protein changes that correlate both with acquired resistance and the MSI/MSS status, and validated these finding using immunodetection techniques. We are currently extending the CRC study to look at multiple resistance mechanisms for 5-FU with other commonly used CRC therapeutics, oxaliplatin and irinotecan.

Legal entity responsible for the study: Dr. Steve Shnyder

Funding: University of Bradford (Institute of Cancer Therapeutics)

Disclosure: All authors have declared no conflicts of interest.

536P Docetaxel, cisplatin, and 5-fluorouracil (DCF) chemotherapy in the treatment of metastatic or unresectable locally recurrent anal squamous cell carcinoma: A phase II study of French interdisciplinary GERCOR and FFCD Groups (Epitopes-HPV02 study)

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Background: Anal Squamous Cell Carcinoma (ASCC) is a rare disease, but its incidence is markedly increasing. To date, in advanced ASCC, no standard regimen exists. We have previously published the potential role of DCF regimen. Among 8 advanced ASCC consecutive patients who relapsed after CRT, the DCF regimen induced a complete response in 4 patients, including 3 pathological complete responses. Thus, this study was designed to confirm the interest of DCF regimen in advanced ASCC patients.

Methods: A multicentre phase II trial was conducted among 25 hospitals in France. Main eligibility criteria were histologically proved unresectable locally advanced recurrent or metastatic ASCC, ECOG-PS <2, and being eligible for DCF. Patients received either 6 cycles of standard DCF or 8 cycles of modified DCF depending on age (> *vs.* < = 75 years-old) and ECOG-PS (0 *vs.* 1). The trial was set up based on a Simon's optimal two-stage design, allowing an early futility interim analysis amid the first 21 patients. The primary endpoint was the observed PFS rate at 12months from the first DCF cycle. A PFS rate above 25% was expected. With a unilateral alpha error of 5% and a statistical power of 90%, 66 evaluable patients had to be included.

Results: 66 patients were enrolled from September 2014 to January 2017. Median age was 60.05 years (range, 38-78) with female predominance (81.8%). 40 (60.6%) patients had locoregional involvement at enrolment, and the most frequent metastatic sites were liver (60.6%), distal lymph node (48.5%), and lung (36.4%). At interim analysis, 10 (47.6%) patients were progression-free at 12 months from the first DCF cycle. To date, 65 patients are assessable for response rate by investigators. The objective response rate is 87.7%, including 36.9% of complete responses. Among the first 32 patients with ≥12 months of follow-up, 15 (46.9%) patients were progression-free at 12 months.

Conclusions: This first ever conducted prospective trial in front-line advanced ASCC demonstrated a high long-lasting response rate of the DCF regimen. DCF regimen should then be considered as a standard of care in this situation.

Clinical trial identification: NCT02402842

Legal entity responsible for the study: University Hospital of Besancon

Funding: Research grant from the University Hospital of Besançon

Disclosure: All authors have declared no conflicts of interest.

537P P2 study of ADXS11-001 Immunotherapy in patients with persistent/recurrent, surgically unresectable locoregional, or metastatic squamous cell anal cancer

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Background: The number of new anal cancer (SCCA) cases in the US has been rising annually; 20% of patients (pts) will develop metastatic (met) disease, which presents an unmet medical need. A large population-based study showed 88% of SCCA were HPV+ and 73% had HPV-16 (Hoots et al IJC 2009). ADXS11-001 (ADXS) is an irreversibly attenuated Listeria monocytogenes immunotherapy that targets HPV-associated cancers. It is bioengineered to secrete an antigen-adjuvant protein fused to the E7 peptide of HPV-16. It allows the generation of tumor antigen specific cytotoxic T cells that infiltrate and destroy tumor cells. This is the 1st P2 trial to assess the efficacy/safety of ADXS in met SCCA.

Methods: This multicenter, open-label, 2-stage design trial (NCT02399813) includes pts ≥ 18 yrs with histologically confirmed, measurable SCCA and previous ≥ 1 line of therapy for advanced disease. Pts received IV ADXS monotherapy ($1x10^9$ colony forming units) every 3 weeks for ≤ 2 years or until a discontinuation criterion was met. Tumor assessments (RECIST 1.1) were every 9 wks. Interim analysis was planned on enrollment of 31 evaluable pts (≥ 1 post-baseline scan). An objective response rate (ORR) ≥ 10% or a 6-month progression free survival (PFS) ≥ 20% with tolerable safety would allow proceeding to Stage 2.

Results: Preliminary Stage 1 results are reported with data from 29 of the planned 31 evaluable pts. Median age 60 yrs, range 43-77; 27 F/2 M; median follow-up time 191 days. One pt (3.5%) had a durable partial response lasting > 6 months (after progression on prior anti-PD-1 therapy) and 7 pts had stable disease (24%). Disease control rate was 28%. The current KM 6-month PFS estimate is 22%. Common (≥ 30%) treatment related AEs (TRAEs) were grade 1-2 chills/rigors, fever, hypotension and vomiting. Grade 3 TRAEs of cytokine related syndrome (n = 1; SAE), infusion related reactions (n = 2; 1 SAE) and hypotension (n = 2; 1 SAE) were reported.

Conclusions: ADXS monotherapy showed promising activity and met the predefined 6-month PFS rate. Treatment was well-tolerated with mostly grade 1-2 infusion related AEs that resolved successfully with standard care. Further investigation is ongoing in this population.

Clinical trial identification: NCT02399813

Legal entity responsible for the study: Advaxis, Inc

Funding: Advaxis, Inc

Disclosure: C. Eng: Consulting agreement with Advaxis. All other authors have declared no conflicts of interest.

538P Relationship between pretreatment levels of circulating DNA, circulating tumor cells, CEA, CA19.9 and tumor burden on CT scan in patients treated for a metastatic colorectal cancer

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Background: Circulating DNA has been reported as prognostic in metastatic colorectal cancer (mCRC) but its correlation with tumor burden has never been clearly established. The aim was to evaluate the correlation between pretreatment levels of circulating tumor DNA (ctDNA), cell-free-DNA (cfDNA), circulating tumor cells (CTC), CEA, CA19.9 with tumor characteristics on CT scan.

Methods: It was a retrospective analysis from a prospective trial on circulating markers (ctDNA, cfDNA, CTC, CEA, CA19.9) at baseline in mCRC patients (NCT01212510). CT scans were centrally reviewed to assess 3 tumor parameters: the diameter using RECIST version 1.1, the total tumor length (TTL) defined as the sum of diameter of all visible lesions, and the volume (Vol) of the main lesion. Relationship between circulating markers and CT scan were analysed as well as progression-free survival (PFS) and overall survival (OS) and prognostic factors using Cox models.

Results: A total of 83 mCRC patients were included. Median baseline ctDNA, cfDNA, CEA, CA19.9 and CTC were 21 (0.12-74) %, 36 (6-2275) ng/mL, 75 (2-64051) ng/ml, 90 (4-70900) UI/mL, and 7 (1-194)/mL, respectively. For CT scan, median value was 81 (11-310) mm for RECIST, 196 (14-1906) mm for TTL and 65 (2-783) $mm^3$for Vol. There was a significant correlation between RECIST and CEA (p = 0.0005), CA19.9 (p = 0.007), cfDNA (p < 0.0001), ctDNA (p = 0.01), between TTL and CEA (p < 0.0001), CA19.9 (p = 0.0008), cfDNA (p < 0.0001), ctDNA (p < 0.0001) and between Vol and CEA (p = 0.008), CA19.9 (p = 0.02), cfDNA (p = 0.0015). The median PFS and OS were significantly increased in patients with low (< vs > to median) CA19.9 (8.8 vs 3.2 m., p = 0.03 and 16.4 vs 9 m., p = 0.01), ctDNA (8 vs 3 m., p = 0.006 and 18.3 vs 8.3 m., p = 0.0001). TTL was only associated with PFS (9 vs 3 m., p = 0.009) and RECIST and Vol with OS (15.3 vs 11.8 m., p = 0.04). In multivariate analysis, RECIST (p = 0.0004), CA19.9 (p = 0.004) and OMS performance status (p = 0.04) were prognostic for OS.

Conclusions: Circulating makers and tumor burden on CT scan were correlated and prognostic. Interventional studies are needed to evaluate the usefulness of circulating makers in decision making.

Clinical trial identification: NCT01212510

Legal entity responsible for the study: Rouen University Hospital

Funding: Merck, Roche and Amgen

Disclosure: All authors have declared no conflicts of interest.

539P Circulating tumor cells (CTCs), molecular alterations and their correlation with characteristics of patients (pts) with metastatic colorectal cancer (mCRC) treated in the Spanish TTD VISNÚ Program

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Background: CTCs, *RAS* and *BRAF* mutations are prognostic factor in mCRC pts. The VISNÚ program was designed to explore the impact of FOLFOXIRI + bevacizumab in a high-risk mCRC group according to CTCs ≥3 (VISNÚ-1) and to compare the efficacy of bevacizumab or cetuximab associated to FOLFIRI in a low-risk group according to CTCs < 3 and RAS wild-type (VISNÚ-2).

Methods: Blood samples for CTCs enumeration by Cell Search® method (Menarini – Silicon Biosystems, Inc) were collected at baseline, and samples of tumor tissue were used to determine *KRAS-NRAS-BRAF-PIK3CA* mutations. This preliminary analysis shows the correlation among CTCs, molecular mutations and clinical characteristics by chi-square analysis.

Results: 1208 pts were screened for CTCs and RAS mutation and 590 of them were eligible for the VISNÚ program. In the screening population, CTCs ≥ 3 was found in 40.8%, RAS, BRAF and PI3K mutations were present in 51.4%, 7.5% and 11.3% of pts respectively. No correlation was found among CTCs and RAS, BRAF and PIK3CA mutations (p 0.29, 0.10 and 0.12 respectively). CTCs ≥ 3 was associated with worse ECOG, stage IV, liver, lung and bone metastases, > 2 metastatic sites and CEA levels > 5 ng/ml. RAS mutation correlated with worse ECOG, stage IV, liver, lung and bone metastases, > 2 metastatic sites and CEA levels > 5 ng/ml. BRAF mutation correlated with primary right colon location, and metastases in peritoneum, lymph nodes, bone and liver and high tendency for female (p = 0.058) (Table). PIK3CA mutation was only associated with right primary location and age > 65 years.

Table: 539P

Parameters	CTCs> 3 p value	RASmut p value	BRAFmut p value
ECOG	0.0069	0.002	–
Primary location	–	–	< 0.0001
Metastatic sites			
Liver	< 0.0001	0.01	0.02*
Lung	0.02	0.005	
Bone	0.0002	0.002	0.002
Peritoneum	–	–	0.004
Lymph nodes	–	–	0.005
N° organ involved	0.001	0.007	–
Stage at diagnosis	0.002	0.02	–
CEA levels	< 0.0001	0.02	–

*BRAF mutant less frequently associated to liver involvement

Conclusions: CTCs and RAS mutation are significantly associated with other clinical poor prognostic factors. The poor prognosis of BRAF-mutated tumors reported in the literature cannot be explained by its correlation with poor prognostic clinical characteristics.

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Legal entity responsible for the study: Spanish Cooperative Group for the Treatment of Digestive Tumors (TTD)

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540P Analysis of liquid biopsies from metastatic colorectal carcinoma (mCRC) patients (pts) enrolled in the CAPRI GOIM clinical trial

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Background: Liquid biopsy can represent an alternative to tissue biopsy for biomarker testing in cancer pts. In addition, liquid biopsy can be used to monitor the response to treatment and the molecular evolution of the disease.

Methods: In the CAPRI GOIM trial, KRAS exon 2 wild type (wt) mCRC pts received first line cetuximab plus FOLFIRI. Tumor samples were assessed by Next Generation Sequencing (NGS) with the Ion AmpliSeq™ Lung and Colon Cancer Panel (Thermofisher). Plasma samples at baseline (n = 96), at 3 weeks of treatment (n = 54), at 6 weeks (n = 14) and at progression of disease (n = 24) were collected from 96 patients and analyzed for exon 2, 3 and 4 KRAS and NRAS mutations using BEAMing Digital PCR (Sysmex Inostics).

Results: Analysis of basal plasma samples from the 96 pts included in this study showed a concordance of 79,2% with the tissue RAS status as defined by NGS. The 11 cases that were RAS mutant (mut) in tissue and wt in plasma had suboptimal plasma volume available for analysis (<3ml), and in 5 cases the only sites of recurrence were lung and/or lymph nodes. Among the 9 cases with wt tissue and RAS mut plasma, all but one had a mutant allelic frequency (MAF) <1%. Plasma samples at 3 weeks were available for 11 pts RAS mut in both tumor and plasma, 6 pts RAS wt in tumor and mut in plasma, and 30 pts with both tissue and plasma samples wt. Within pts with RAS mutations in both tumor and plasma, a significant reduction in plasma RAS MAF was observed in all cases at 3 weeks. However, an increase in RAS MAF was observed in all available samples (n = 4) at the progression of the disease. A reduction of MAF after 3 weeks of treatment was also observed in pts who had a RAS positive liquid biopsy with a negative tissue. Among pts with both tissue and plasma basal samples wt, RAS mutations were found in only 1 (3,3%) case after 3 weeks of treatment and in none of the 8 available plasma samples at 6 weeks.

Conclusions: These data suggest that liquid biopsy might better recapitulate the heterogeneity of mCRC and might be useful to monitor the response to therapy. Analysis are ongoing to evaluate the clinical significance of RAS mutations with low MAF.

Clinical trial identification: Eudract number: 2009-014041-81

Legal entity responsible for the study: Nicola Normanno

Funding: Merck Serono, Sysmex Inostics

Disclosure: N. Normanno: Participation to advisory boards and/or research funding from Amgen, AstraZeneca, Merck Serono, MSD, Qiagen, Roche, Sysmex. E. Martinelli, T. Troiani: Participation to advisory boards: Servier and Roche. E. Maiello: Participation to advisory boards: Merck Serono, Roche, Sanofi. F. Ciardiello: Participation to advisory boards and/or research funding from Amgen, Bayer, AstraZeneca, Merck Serono, Roche. All other authors have declared no conflicts of interest.

541P Circulating cell-free DNA as predictor of treatment failure after neoadjuvant chemoradiotherapy before surgery in patients with locally advanced rectal cancer

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Background: Treatment of patients with locally advanced rectal cancer (LARC) is based on a combination of chemo-radiotherapy (CRT) and surgery. The rate of distant recurrences remains over 25% and biomarkers to detect treatment failure are urgently needed. Circulating cell-free DNA (cfDNA) in plasma is a mixture of normal and cancer specific DNA segments, and a promising biomarker in patients with colorectal cancer. Only few studies have examined the potential utility of cfDNA in LARC but suggest a correlation between cfDNA and the response to neoadjuvant CRT. The aim of our study was to investigate plasma cfDNA in patients with LARC treated with induction chemotherapy (ICT), CRT and surgery.

Methods: A total of 124 patients with LARC were prospectivily included at Herlev Hospital, Denmark, from 2010-14. Patients were treated with neoadjuvant CRT and 52 also received 1-3 cycles of ICT with CAPEOX. Total cfDNA levels were measured by direct fluorescent assay in plasma samples obtained at baseline, after ICT and after CRT. Mann-Whitney test, Kaplan-Meier plots and Cox regression analysis were used for statistical analyses. Disease free survival (DFS) was measured from start until distant recurrence or death from any cause.

Results: Median baseline level of cfDNA was 0.96 ng/μL (range 0.46-2.28). Baseline cfDNA did not differ between stage II & III disease (p = 0.15). Median follow-up was 54 months and 27.4% of the patients had distant recurrence during follow-up. When dividing patients in groups of cfDNA quartiles, increasing cfDNA levels were associated with impaired outcome. Patients with baseline cfDNA levels above the 75th quartile, had a higher risk of distant recurrence and shorter median RFS compared to those below, (HR 2.63; CI95%: 1.34-5.15; p = 0.008). The same applied to DFS (HR 1.97, CI95%: 1.09-1.97, p = 0.003). High cfDNA level after CRT was associated with an increased risk of distant recurrence (p = 0.052).

Conclusions: Our results demonstrate a strong correlation between high baseline level of cfDNA and increased risk of distant recurrence in patients with LARC treated with neo-adjuvant CRT. Consequently, cfDNA could hold potential for better pre-treatment risk assessment and as tool for individualized therapy in this setting.

Legal entity responsible for the study: Jakob Vasehus Schou

Funding: None

Disclosure: All authors have declared no conflicts of interest.

542P Circulating tumor (ct) DNA captures intrapatient heterogeneity in metastatic colorectal (mCRC) patients (pts) progressing to FOLFIRI+panitumumab

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Background: CRC cells evade EGFR blockade by several mechanisms of acquired resistance, mainly mutations in RAS, EGFR ECD, HER2 and MET. ctDNA is shed into the bloodstream by tumor cells and can be effectively used to track tumor heterogeneity and to evaluate acquired mutations at tumor progression.

Methods: We included mCRC pts treated in a phase II study of FOLFIRI + panitumumab in irinotecan-refractory mCRC. ctDNA was collected at the end of treatment, processed with the Oncomine colon ctDNA Assay, and sequenced in the PGM Ion Torrent NGS System. The detectable cutoff mutation was 0.1%. Subclonal mutations were defined as mutations with mutant allele fraction (MAF) $\leq$ 50% of the greatest somatic MAF in the sample. Baseline mutations were analyzed in tumor tissue by dPCR.

Results: ctDNA from 16 pts was analyzed. Clinical characteristics of pts were 69% male; median age 61.5 years; 75% left vs 25% right colon. At least one mutation was detected in 94% of pts (15/16); median mutations per sample was 2.5 (range 1 -13). The frequency of detected mutations was: 13 TP53, 3 APC, 1 CTNNB1, 15 KRAS, 8 NRAS, 7 EGFR, 4 BRAF, 4 PIK3CA, 4 MAP2K1, 1 GNAS, 1SMAD4. While TP53, APC, PIK3CA

and BRAF were most likely to be clonal, EGFR, MAP2K1, RAS were generally subclonal. All EGFR ECD mutations emerged in the left colon and all co-existed with RAS mutations plus at least one additional acquired mutation (median 6, range 3-11). RAS/BRAF mutations emerged in 100% and 66% of right and left colon respectively, and co-existed with other acquired mutations in 72% of cases (median 3, range 1-11) Best response was: PR 8 pts, SD 6 pts and PD 2. In both pts with PD only one acquired mutation was detected at progression (PIK3CA and KRAS respectively), and both mutations were detected in the matching pre-treatment tissue and plasma sample at low MAF. Pts follow-up is ongoing, correlation between mutational profile and response to treatment will be presented.

Conclusions: ctDNA analysis captured intrapatient heterogeneity that developed as a result of EGFR inhibition. All EGFR ECD mutations emerged in the left colon and always co-existed with several other mechanisms of acquired resistance, reflecting genomic complexity.

Clinical trial identification: NCT01704703

Legal entity responsible for the study: Spanish Cooperative Group for the Treatment of Digestive Tumors (TTD)

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543P Dynamic changes in levels of gene mutations using circulating tumor DNA (ctDNA) and efficacy of 1st-line modified (m)-FOLFOXIRI plus bevacizumab (bev) for metastatic colorectal cancer (mCRC) harboring RAS mutation (mt) (JACCRO CC-11)

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Background: FOLFOXIRI plus bev is a standard initial therapy for mCRC but toxic in Japanese patients (pts) due to frequent febrile neutropenia (FN). We performed a phase II trial to assess the safety and activity of 1st-line m-FOLFOXIRI plus bev for mCRC with RAS mt. In addition, pre-planned analysis of a number of genes in ctDNA during therapy that might be determinants of therapeutic efficacy was performed.

Methods: Pts with unresectable/measurable tumors received bev and 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]. After induction therapy for a maximum of 12 cycles, maintenance therapy with fluorouracil/LV plus bev was administered. The primary endpoint was objective response rate (ORR). Progression-free survival (PFS), overall survival, early tumor shrinkage (ETS), depth of response (DpR), and safety were secondary endpoints. Plasma samples for extraction of ctDNA were collected at 3 points (pre-, 8w, and progression) and analyzed for specific KRAS, NRAS, BRAF, and PIK3CA variants with real-time PCR assays.

Results: Sixty-two of 64 participants evaluable for efficacy had the following characteristics: median age 63, 55% male, 92% PS0, and 27% right-sided tumors. Median follow-up time was 7.9 months. ORR and disease control rate were 74.2% and 96.8%, respectively. ETS was 74%, and median DpR was 48%. Median PFS was not reached. Common grade 3 or 4 adverse events were neutropenia (49%), hypertension (22%), diarrhea (13%), and FN (4.8%). No treatment-related deaths occurred. Analysis of ctDNA from pre-treatment plasma confirmed mts in 72% (38/53) of pts. Absence of mt at 8w correlated with ORR regardless of mt status at pre-treatment [no mt; 80% (32/40), any mt; 45% (5/11), P = 0.05, t-test]; moreover, pts with PIK3CA mt at pre-treatment had a poor response (43%, 3/7).

Conclusions: m-FOLFOXIRI plus bev is active and feasible for Japanese mCRC pts with RAS mt. *KRAS*, *NRAS*, and *PIK3CA* mt in ctDNA were associated with response to the triplet plus bev and might potentially be used to predict outcomes.

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Legal entity responsible for the study: Japan Clinical Cancer Research Organization: JACCRO

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544P The frequency of RAS mutation in circulating tumor DNA predicts worse survival in patients with mCRC

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Background: RAS mutations predict a worse prognosis in metastatic colorectal cancer(mCRC). However, there are few findings regarding the prognostic value of RAS mutations in circulating tumor DNA (ctDNA). We aimed to compare the concordance of genomic alterations between ctDNA and tissue biopsies and assess the prognostic value of RAS mutations in ctDNA.

Methods: Gene mutational status in plasma and tissue were evaluated in mCRC patients by next-generation sequencing (NGS). Kaplan-Meier curve and Cox regression model were used to compare the progressive free survival (PFS) between different level of RAS mutations frequency.

Results: of NGS testing from tumor tissue and ctDNA from 110 sequential mCRC patients were compared. Analysis of 6 gene in baseline tissue and plasma samples showed a 67.3% overall agreement. Concordance between the two platforms for KRAS, NRAS, BRAF, PIK3CA, SMAD4 and FBXW7 mutations, were 80.0%, 98.2%,97.2%,91.8%,69.1%,93.6% and 96.4%, respectively. RAS mutation rate in tissue and ctDNA were 48.1% and 29.1%. Fifty-nine patients were detected RAS mutation in tumor tissue, only thirty-six patients with plasma RAS mutation. One patient was detected ctDNA RAS mutation without mutation in tissue. Across plasma RAS gene, sensitivity and specificity were 61.0% and 99.3%, respectively. With a 48.2% cut-off rate, we divided 59 tissue RAS mutation patients into two different ctDNA RAS mutation groups(high frequency and low frequency group. Median PFS in high frequency group was 1.9 months and in low frequency group was 4.8 months(P = 0.002). In multivariate analysis considering other clinical factors(i.e. synchronous or metachronous metastasis, solitary and multiple metastases and CEA level, high ctDNA KRAS mutation frequency was independent adverse prognostic factor (HR 4.09,95% CI 1.61-10.40,p=0.003) for PFS in tissue KRAS mutation patients.

Conclusions: Plasma and tissue NGS testing have a high concordance in genomic alterations. Higher rate of baseline KRAS mutation frequency predicts worse prognosis in mCRC. Both plasma and tissue NGS may be necessary to describe the complex biology of mCRC.Circulating tumor DNA testing could be a viable alternative for genotyping of mCRC and recommended for routine clinical practice.

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545P Epidermal growth factor receptor (EGFR) copy number (CN) as a biomarker of prognosis and panitumumab (Pan) benefit in RAS-wt advanced colorectal cancer (aCRC)

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Background: Whilst RAS mutations predict which aCRC patients (pts) will not benefit from anti-EGFR agents, RAS-wt status does not reliably predict who will. Several studies report that high EGFR ligand expression (EREG/AREG) is predictive of anti-EGFR agent benefit but progression towards clinical utility is limited by lack of consensus on a clinical dichotomisation point and additional tumor material required. Here we explore EGFR copy number as a biomarker of prognosis and predictor of Pan benefit in a randomised trial in aCRC.

Methods: EGFR CN, EREG/AREG RNA expression, *RAS/RAF* mutations were assessed in tumor from 275 pts randomised to 2nd-line irinotecan (Ir) or IrPan (PICCOLO, *Lancet Onc* 14:749-59). EGFR CN status was measured by the Affymetrix OncoScan array, analysed using Biodiscovery Nexus software and defined as normal (2 copies) or gain (>2 copies). Prognostic analysis was in Ir alone pts. Predictive analysis, in the 234 *RAS*-wt pts, compared baseline values with outcomes using Cox proportional hazards models.

Results: 196 (71.3%) pts were classified as EGFR gain and 79 (28.7%) as normal. EGFR gain was significantly associated with high EREG and AREG RNA expression (both $p < 0.001$). EGFR gain was not prognostic for OS ($p = 0.97$) or PFS ($p = 0.98$). However, it was predictive of Pan benefit: in *RAS*-wt pts with EGFR gain, median PFS was 5.7 mo (IrPan) vs 3.7 mo (Ir) (HR = 0.60[0.43-0.83], $p = 0.002$), but pts with normal EGFR had no benefit: 3.4 mo (IrPan) vs 2.9 mo (Ir) (HR = 1.23[0.72-2.08], $p = 0.45$); interaction $p = 0.02$. Significant PFS biomarker/treatment interaction was also seen in all 275 pts, including *RAS* or *RAF* mutants ($p = 0.01$). In *RAS*-wt pts EGFR gain was associated with higher response rates than normal with IrPan (45.3% vs 18.7%, $p = 0.01$) but not with Ir (13.3% vs 12.9%, $p = 1.0$). Interaction was not significant ($p = 0.22$) or for OS ($p = 0.20$).

Conclusions: EGFR CN status may allow for further stratification for Pan benefit in *RAS*-wt patients. Normal EGFR CN status identified nearly 1/3 of pts without Pan benefit. This biomarker is consistent with EGFR ligand data, and is a DNA-based assay with a clearly definable dichotomised cut-point and therefore is of potential clinical utility.

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Legal entity responsible for the study: University of Leeds

Funding: Affymetrix

Disclosure: All authors have declared no conflicts of interest.

546P Survival analysis of KRAS, NRAS, BRAF, PIK3CA wild type (wt) metastatic colorectal cancer (mCRC) patients (pts) treated with FOLFIRI plus cetuximab in the CAPRI- GOIM trial

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Background: The CAPRI-GOIM trial consisted of two parts: FOLFIRI plus cetuximab in first line followed by cetuximab plus FOLFOX as second line treatment for molecularly selected mCRC pts. The primary endpoint was progression-free survival (PFS). Secondary endpoints included overall survival (OS), response rate and safety. This is an updated analysis providing the mature results for OS in KRAS, NRAS, BRAF, PIK3CA wt pts.

Methods: In the CAPRI-GOIM trial 340 mCRC pts with KRAS exon 2 wt tumors were treated in first line with FOLFIRI plus cetuximab until disease progression or unacceptable toxicity. After first line therapy progression, pts (157), who achieved a clinical response with first line treatment, were randomized to FOLFOX plus cetuximab (Arm A) or to FOLFOX (Arm B). Archival tissue samples from primary tumours were centrally assessed by next generation sequencing (NGS) with the Ion AmpliSeq Colon and Lung cancer panel. Here we report mature survival data at median follow-up of 69 months (m) (cut off date: April 30, 2017) for 98 out of the 124 RAS wt patients with NGS analysis, that were representative of the 340 intention to treat patient population.

Results: Median OS for these 98 pts was 34.0 m (95% CI 30.2–37.8) with PFS of 11.7 m (95% CI 10.3–13.1). Eighty six out of 98 pts had tumors that were KRAS, NRAS, BRAF, PIK3CA wt. In this cohort, OS was 35.8 m (95% CI 29.9–41.9) with PFS of 12.3 m (95% CI 10.7–14.0). PFS and OS were also evaluated according to tumour location (see Table for results).

Table: 546P

Cohort	Median OS (months)		Median PFS (months)	
	Right	Left	Right	Left
RAS wt (n = 98)	33.4 (31.7-34.9)	35.8 (29.9-41.7)	9.9 (7.9-12.0)	12.3 (11.0-13.6)
KRAS, NRAS, BRAF, PIK3CA wt (n = 86)	34.0 (22.1-46.0)	35.8 (29.5-42.3)	9.9 (5.3-14.6)	12.3 (10.7-14.0)

Conclusions: Long-term follow-up analysis of pts enrolled in the CAPRI-GOIM trial showed a median OS of approximately 36 m in KRAS, NRAS, BRAF and PIK3CA wt pts. A better prognostic outcome in terms of OS and PFS was observed in left-sided as compared to right-sided tumors.

Clinical trial identification: EudraCT number 2009-014041-81

Legal entity responsible for the study: Gruppo Oncologico dell'Italia Meridionale (GOIM)

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Disclosure: E. Martinelli: Advisory Board: Merck serono, Amgen. F. Ciardiello: Advisory Board: Merck Serono, Roche, Amgen, Pfizer, Bayer, Lilly. All other authors have declared no conflicts of interest.

547P ULTRA clinical trial: Prospective comparative clinical outcome analysis of three different RAS/BRAF sensitivity mutational cut-offs. A Phase II study of the Spanish TTD Group

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Background: In metastatic colorectal cancer (mCRC) recent studies have shown the importance to accurately quantify low-abundance mutations of RAS pathway because response to anti-EGFR therapy may depend on certain mutation thresholds. We designed a clinical trial to compare clinical outcomes of patients selected with different analytical sensitivity thresholds for RAS/BRAF mutated alleles using a highly sensitive and quantitative technique of digital PCR (dPCR).

Methods: Hotspots including RAS (KRAS and NRAS exons 2/3/4) and BRAF (exon 15) were prospectively analyzed in tumour FFPE samples from 61 patients with mCRC included in the ULTRA trial. Patients had received one or two previous chemotherapy lines and were deemed resistant to irinotecan. Response rate (RR), progression-free survival (PFS) and overall survival (OS) were correlated with the mutational status based on three different cut-off points (0.1%, 1% and 5%).

Results: The overall RR was 51.7% and comparative analysis of clinical outcomes translated into a differential progression free survival (PFS), response rate (RR) and progression disease (PD) in the different cohorts defined by the 3 selected analytical sensitivity cut-off points (Table). PFS prediction was higher when we considered a threshold of 5% in RAS/BRAF scenario (HR mut vs wt = 3.85; CI95% [1.16-12.82], $p = 0.018$).

Conclusions: Optimal sensitivity RAS/BRAF mutational analysis cut-off for clinical outcome prediction lies between 1 and 5% (closer to 5%). Increasing analytical sensitivity worsens patient's selection. Further sensitivity threshold comparative analysis will define an optimal cut-off.

Table: 547P

			Highly-sensitive digital PCR		
			cut-off 0.1%	**cut-off 1**%	**cut-off 5**%
RAS + BRAF	mut/wt (n/n)		14/47	8/53	3/58
	RR % (mut/wt)		46.2/52.1	37.5/52.8	33.3/51.7
	SD % (mut/wt)		46.2/33.3	50.0/34.0	33.3/36.2
	PD % (mut/wt)		7.7/12.5	12.5/11.3	33.3/10.3
	PFS months	median (mut/wt)	9.3/7.6	7.4/7.6	4.0/8.8
		HR (mut vs wt)	0.82	0.77	3.85
		HR (95%CI)	0.43-1.56	0.35-1.69	1.16-12.82
		P-value	0.500	0.510	**0.018**
	OS months	median (mut/wt)	17.4/12.5	26,22/13.88	16.05/16.18
		HR (mut vs wt)	0.552	0.542	1.57
		HR (95%CI)	0.24-1.25	0.19-1.54	0.48-5.11
		P-value	0.153	0.250	0.46

Clinical trial identification: NCT01704703

Legal entity responsible for the study: Spanish Cooperative Group for the Treatment of Digestive Tumors (TTD)

Funding: Public funding from the Spanish Ministry of Health, Social Policy and Equality. (Trial Ref: EC11-050)

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548P Prognostic impact of BRAF and KRAS mutations according to the consensus molecular subtypes of colorectal cancer

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Background: In the present study we report the distribution and prognostic impact of KRAS and BRAF mutations according to microsatellite instability (MSI) status and consensus molecular subtypes (CMS) in colorectal cancer (CRC).

Methods: A total of 1197 primary tumor samples from a consecutive series of patients treated surgically for stage I-IV CRC at Oslo University Hospital, Norway, were included in the study. Comprehensive clinical and pathological data were prospectively collected for all patients. Mutation analyses were performed for hotspots in KRAS (exon 2: codon 12 and 13, exon 3: codon 61) and BRAF (exon 15: codon 600) and MSI-status was determined. A subset of samples were analyzed for gene expression using exon-level microarrays and classified according to the CMS groups of CRC, with confident classification obtained in 317 samples. To increase the number of samples with CMS classification the analysis was supplemented with gene expression data for 514 patients in the publically available dataset GSE39582, including also MSI status, BRAF and KRAS mutation status, as well as clinical data. Gene expression signatures previously shown to be associated with BRAF and KRAS mutations, respectively, were used to evaluate differential impact of mutations on gene expression among CMS groups.

Results: $BRAF^{V600E}$ and KRAS mutations are shown to have inferior relapse-free survival in MSS tumors exclusively (BRAF mut vs KRAS/BRAF wt: Hazard ratio (HR) 2,35 (1,71-3,22); $p < 0,001$ and KRAS mut vs KRAS/BRAF wt: HR 1,23 (1,01-1,49); $p = 0,044$). Stratifying the survival analysis according to CMS groups reveals the negative prognostic impact of $BRAF^{V600E}$ mutations to be specific to MSS tumors in CMS1 (BRAF mut vs wt: HR 4,96 (1,74-14,12); $p = 0,003$), while KRAS mutations are associated with poor prognosis distinctively in MSS tumors in CMS2 (KRAS mut vs wt: HR 1,60 (1,11-2,30); $p = 0,011$). Further, the effects of BRAF and KRAS mutations on gene expression signatures are shown to vary according to MSI-status and CMS subtype, substantiating the subtype-specific prognostic associations.

Conclusions: *$BRAF^{V600E}$* mutations have poor prognostic value specific to MSS tumors in CMS1, while *KRAS* mutations are associated with adverse outcome in MSS tumors in CMS2.

Legal entity responsible for the study: Oslo University Hospital

Funding: Norwegian Cancer Society, Research Council of Norway, Southern and Eastern Norway Regional Health Authority

Disclosure: All authors have declared no conflicts of interest.

549P Gene expression signatures in BRAF V600E mutant colorectal cancer in relation to WNT signaling cascade

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Background: Colorectal cancers (CRC) with BRAF V600E mutations have typically shown poor outcomes in several clinical trials, but its biological role has not been fully elucidated. Classification of CRCs according to gene expression profiling and methylome analysis remains controversial with regards to their ability to stratify patients for precision therapy.

Methods: We performed mRNA microarray analysis and used pathway analyses by Gene Set Enrichment Analysis (GSEA) in the following three subsets; eight BRAF-mutant CRC tissues without MSI, six BRAF-mutant CRCs with MSI and five BRAF-wild type CRCs with MSI. Following identification of candidate biomarkers that affect poor outcomes and associate with BRAF V600E mutation, we examined epigenetic variations of these candidate biomarkers in a cohort of 1068 CRC patients who underwent surgical resection of their primary tumor and/or metastatic lesions from 1994 to 2015 at the Okayama University Hospital.

Results: Prominent signatures enriched in CRCs with BRAF V600E mutation were EMT-related processes (EMT and myogenesis), Wnt signaling and intestinal differentiation-related genes. Among the differentially expressed genes, Wnt-antagonist, Secreted frizzled-related proteins (SFRPs) were significantly upregulated in CRCs with BRAF V600E mutation especially without MSI. As SFRPs are well known to be inactivated by promoter hypermethylation, and up to 80% of CRCs are methylated in the promoter region of the SFRP2 gene, we speculated and analyzed SFRP2 promoter methylation status in 993 CRCs of our cohort by a modified highly sensitive assay for bisulfite DNA followed by fluorescence-based PCR, as we previously reported (JNCI 2009). SFRP2 methylation was observed in 647 (65.2%). Interestingly, SFRP2 unmethylated CRCs with genetic mutation in the KRAS/BRAF genes demonstrated significantly poorer outcome in RFS compared with SFRP2 methylated CRCs with genetic mutations in the KRAS/BRAF genes (5-yrs RFS: 59.0% vs 80.4%, $P < 0.001$, HR: 2.07 [95% CI, 1.19 to 3.48], $P = 0.01$).

Conclusions: Our results suggest that SFRP2 methylation status could be a potential prognostic biomarker for CRCs, especially with genetic mutations in the KRAS/BRAF genes.

Legal entity responsible for the study: Department of Gastroenterological Surgery, Okayama University

Funding: None

Disclosure: All authors have declared no conflicts of interest.

550P Prognostic significance of BRAF mutation-associated gene signature in colorectal cancer

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Background: BRAF mutation is associated with poor survival in colorectal cancer. We aimed to generate genomic signature associated with BRAF mutation that possibly predict prognosis in colorectal cancer.

Methods: A gene expression signature reflecting BRAF mutation was generated in TCGA cohorts (n = 207). The colorectal cancer patients were stratified into two groups according to this signature: BRAF mutation type colorectal cancer or BRAF wild type colorectal cancer. Prognostic significance of BRAF mutation-associated gene signature was tested in two other cohorts (GSE 17538, GSE 14333).

Results: The BRAF mutation signature was associated with poor prognosis in two independent cohorts (total n = 522). BRAF mutation signature was associated with poor disease-free survival (median: not reached, P = 0.0303) in GSE14333, and associated with poor overall survival (BRAF mutation vs. wild, P = 0.019 median, 37.310 vs. 134.860 months), and disease-free survival in GSE 17538 (BRAF mutation vs. wild, P = 0.027, median 36.9 months vs. not reached). In a multivariate analysis, BRAF mutation signature was independent poor prognostic factor for disease-free survival (hazard ratio 2.1; 95% CI 1.43-2.62: P = 0.001). Gene network analyses suggested epithelial-mesenchymal transition is the possible explanation for poor prognosis of BRAF mutation colorectal cancer.

Conclusions: BRAF mutation signature is highly associated with poor prognosis in colorectal cancer and the molecules associated with epithelial-mesenchymal transition can be potential treatment targets in BRAF mutation colorectal cancer.

Legal entity responsible for the study: Chonnam National University Hwasun Hospital

Funding: None

Disclosure: All authors have declared no conflicts of interest.

551P Comparative and multimodal analysis of the EGFR, HER2, c-MYC, and MET copy number alteration using in situ hybridization in Korean colorectal cancer patients with integration of array-based copy number data from The Cancer Genome Atlas

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Background: The purpose of this study was to explore gene copy number (GCN) variation of *EGFR*, *HER2*, *c-MYC*, and *MET* in patients with primary colorectal cancer (CRC).

Methods: Dual-colour silver-enhanced in situ hybridization was performed in tissue samples of 334 primary CRC patients. The amplification status (GCN ratio ≥2) and GCN gain (average GCN ≥4) data for the EGFR, HER2, c-MYC and MET genes were obtained. GCN variation was also assessed by the criterion of the 2013 ASCO/CAP guidelines for HER2 testing. The publicly available genetic data of 257 CRC cases from The Cancer Genome Atlas (TCGA) were used for comparative analysis.

Results: Amplification of *EGFR*, *HER2*, *c-MYC* and *MET* was detected in 8 (2.4%), 20 (6.0%), 29 (8.7%), and 14 (4.2%) patients, respectively. Of 66 patients with at least one amplified gene (*HER2-MET* co-amplification: two patients; *HER2-c-MYC* co-amplification: two patients; *EGFR-c-MYC* co-amplification: one patient). There were 109 patients with GCN gains of one or more genes (*EGFR*: 11/334, *HER2*: 29/334, *c-MYC*; 60/334, *MET*: 48/334) and 32.1% (35/109) had multiple GCN gains. When each GCN was assessed by the criterion of the ASCO/CAP 2013 guideline for HER2 testing, 116 people showed positive or equivocal results for one or more genes. The cumulative amplification status had no association with patients' outcome. However, the cumulative results of the GCN gain and GCN status determined according to the ASCO/CAP guideline had a significant prognostic correlation in the univariate (*P* values of 0.006 and 0.022, respectively) and multivariate analysis (*P* values of 0.010 and 0.017, respectively). In analysis of TCGA data, high-level amplification of EGFR, HER2, c-MYC, and MET was observed in 1 (0.4%), 8 (3.1%), 11 (4.3%) and 1 (0.4%) cases, respectively. Copy number alteration status had no prognostic association in TCGA cohort.

Conclusions: In this study, we evaluated GCN variation of four genes in a large sample of Korean CRC patients. The amplification status was not related to patient outcome. However, the GCN gain and GCN status according to the ASCO/CAP 2013 guideline were independent prognostic factors.

Legal entity responsible for the study: Individual

Funding: Korea Health Industry Development Institute (KHIDI)(grant number: HI14C1813)

Disclosure: All authors have declared no conflicts of interest.

552P Mutational status and metastatic patteRn in a cohort Of ADvanced colorectal cancer (aCRC) patients (pts): The ROAD study

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Background: Somatic mutation status in aCRC is becoming increasingly relevant as it may predict efficacy of biological therapies but also site-specific patterns of metastatic spread and outcome.

Methods: We retrospectively analysed a cohort of 640 consecutive aCRC pts diagnosed at University Hospital of Udine, Italy, from 1st January 2000 to 15th March 2017. KRAS, NRAS, BRAF and PIK3CA status was all locally determined by pyrosequencing and/or mass-Spectrometry Assay, with commercially available kits (diatech pharmacogenetics). Pearson's X^2 test was performed with uni- and multivariate models to test association of mutational status and site-specific metastatic spread at the time of diagnosis, death or last follow-up.

Results: Overall, we detected 283 (47%) KRAS mutations, 21 (4%) NRAS mutations, 40 (7%) BRAF mutations, and 61 (14%) PIK3CA mutations. Most common mutations in KRAS gene were located in exon 2 (86%), while about 3% of mutations involved exon 3 and 5% exon 4. NRAS mutations involved equally exons 2 and 3. All BRAF mutated tumours except for one, exhibited exon 15 V600E mutations. Pts with KRAS mutations had an increased risk to develop lung metastases (odds ratio, OR 2.56, 95% CI 1.76-3.71; p < 0.001, in multivariate analyses) or central nervous system metastases (OR 2.58, 95% CI 1.15-5.76; p = 0.021, in univariate model). Instead, pts harbouring BRAF mutations had higher risk of peritoneal (OR 3.05, 95% CI 1.56-5.96, p = 0.001) and nodal (OR 2.20, 95% CI 1.21-4.66, p = 0.012) spread, in uni- and multivariate models, respectively. Liver metastases were not associated with a specific mutational status. Moreover, no associations between NRAS or PIK3CA status and metastatic sites were found.

Conclusions: Our findings suggest that molecular biology may help predicting the metastatic spread in aCRC pts. If confirmed by further studies, these observations could translate into tailored surveillance and follow-up protocols.

Legal entity responsible for the study: University and General Hospital of Udine, Italy

Funding: None

Disclosure: All authors have declared no conflicts of interest.

553P First-line panitumumab (P) plus capecitabine (C) for the treatment of elderly patients (pts) with wild-type KRAS metastatic colorectal cancer (mCRC): Preliminary results of the phase II, PANEL GITuD-2011-01 study

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Background: Despite the high prevalence of CRC in elderly pts (Siegel R et al. 2014), they have been underrepresented in clinical trials (Hutchins LF et al. 1999) and their optimal treatment is yet to be determined. Here, we present the preliminary results of PANEL, a multicenter, single arm, phase II study in elderly pts with WT KRAS mCRC treated with P+C as first-line regimen.

Methods: Pts (≥70 years; ECOG-PS ≤ 2) received P (9 mg/kg, day 1 and q3w) plus C (850 mg/m^2 BID, days 1-14 of a 3 wks cycle) until disease progression or unacceptable toxicity. Response was evaluated every 9 wks according to RECIST 1.1. The outcome measures were: objective response rate (ORR), duration of response (DoR), time to response (TTR), to progression (TTP) and to treatment failure (TTF), progression-free survival (PFS), overall survival (OS), and safety.

Results: 26 pts (11 women; median age: 78 years; ECOG PS: 0 [27%]/1 [65%]/2 [8%]; median serum carcinoembryonic antigen: 25.2 ng/ml [IQR: 93.5]; median lactate

dehydrogenase: 340 U/L [IQR: 195]) received a mean (SD) of 8.3 (5.5) P cycles and 7.7 (4.8) C cycles. 81% and 62% of pts received ≥80% of relative dose intensity of P and C, respectively. Confirmed ORR was 38%, with 69% of pts achieving at least stable disease. Median (95%CI) DoR was 8.7 (6.2-12.7) months, and median TTR was 2.2 (1.8-3.2) months. Median (95%CI) TTP was 9.9 (5.3-12.0) months, with a median TTF of 5.4 (3.1-9.1) months. The median (95%CI) PFS was 9.6 (5.3-11.5) months, and the median OS was 23.7 (12.0-27.5) months. 14 (54%) pts reported grade 3/4 adverse events (Table). There were no cases of neutropenia, trombopenia or toxic deaths.

Table: 553P Incidence of adverse events

	Grade 1-2, N (%)	Grade 3, N (%)	Grade 4, N (%)
Anemia	3 (12%)		
Paronychia	2 (8%)	2 (8%)	
Rash	3 (12%)	1 (4%)	
Mucositis	5 (19%)		
Skin toxicity	10 (39%)	4 (15%)	
Diarrhea	4 (15%)	1 (4%)	
Hand-Foot Syndrome	1 (4%)	2 (8%)	
Hypomagnesemia	4 (15%)		1 (4%)

Conclusions: These preliminary results suggest that panitumumab plus capecitabine is a safe and effective regimen in elderly patients with WT KRAS mCRC.

Clinical trial identification: The number of trial protocol: 2012-000751-13 The realase date (when it was obtained): 2012-06-18

Legal entity responsible for the study: Amgen

Funding: Amgen

Disclosure: All authors have declared no conflicts of interest.

554P Prevalence of KRAS/NRAS/BRAF mutations detected by massive parallel sequencing and differential outcomes in MCRC patients (pts) treated with first line FIr-B/FOx adding bevacizumab (BEV) to triplet chemotherapy

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Background: KRAS/*NRAS*/*BRAF* genotypes guide tailoring of first and subsequent lines of MCRC treatment strategy. First line triplet chemotherapy/BEV regimens significantly improved progression-free survival (PFS) and overall survival (OS) in MCRC patients. OS may be significantly worse in *KRAS* c.35 G > A and *BRAF* mutant (mut) MCRC. Prevalence and differential clinical outcome according to *KRAS*/*NRAS*/*BRAF* genotype was evaluated in MCRC patients treated with FIr-B/FOx intensive regimen.

Methods: Tumoral samples of 67 MCRC pts treated with FIr-B/FOx (77% overall) were analyzed through a 50 genes panel (PGM/Colon Lung Cancer) by ION Torrent. *KRAS* exons 2-4 ($KRAS_{2-4}$), *NRAS* exons 2-4 ($NRAS_{2-4}$), and *BRAF* exon 15 ($BRAF_{15}$) were evaluated. Molecular diagnostic criteria for mutation detection: >500× sequence coverage; >1% mutant allelic fraction. Clinical outcomes (PFS and OS) were evaluated and compared by log-rank.

Results: $KRAS_{2-4}$ mut were 42 (66.7%), 4 not evaluable; $NRAS_{2-4}$mut 13 (19.4%); $BRAF_{15}$ mut 5 (7.5%). $KRAS_{2-4}$/$NRAS_{2-4}$/$BRAF_{15}$ mut MCRC patients were 49 (77.8%), wt 14 (22.2%): single gene mut 40 (63.5%), $KRAS_{2-4}$34 (54%), and $NRAS_{2-4}$ 6 (9.5%); >1 mut genes 9 (14.3%), double mut 5 and triple mut 4, specifically double *KRAS 1*, *KRAS*/*NRAS* 2, *KRAS*/*BRAF* 1, *NRAS*/*BRAF* 1, double *KRAS*/*NRAS* 1, *KRAS*/*NRAS*/*BRAF* 3. $BRAF_{15}$ mut were all atypical and concomitant with *KRAS* and/or *NRAS* mutations. Prevalence of $KRAS_{2-4}$, $NRAS_{2-4}$, $BRAF_{15}$ >1 mut samples were 19%, 53.8%, and 100% of each mut gene. At median follow-up 21 months (m), PFS and OS overall, and of $KRAS_2$ genotype were consistent with previously reported; in c.35 G > A $KRAS_2$ mut trendly worse PFS 8 m and OS 14m. Differential clinical outcome of MCRC patients wt and mut were not significantly different: $KRAS_{2-4}$, PFS 13 and 12m, OS 27m equivalently; $NRAS_{2-4}$, PFS 16 and 12m, OS 28 and 22m; $BRAF_{15}$ PFS 14 and 8 m, OS 28 and 11 m; $KRAS_{2-4}$/$NRAS_{2-4}$/$BRAF_{15}$ PFS 18 and 12m, OS 28 and 22m.

Conclusions: Clinical outcome of MCRC patients treated with FIr-B/FOx is not significantly affected by $KRAS_{2-4}$/$NRAS_{2-4}$/$BRAF_{15}$ genotype; efficacy may be increased in triple wt patients; the prevalent c.35 G > A $KRAS_2$ and $BRAF_{15}$ mut may show worse prognosis.

Legal entity responsible for the study: Enrico Ricevuto

Funding: None

Disclosure: All authors have declared no conflicts of interest.

555P Analysis of angiogenesis biomarkers for ramucirumab (RAM) efficacy in patients with metastatic colorectal cancer (mCRC) from RAISE, a global, randomized, double-blind, Phase 3 study

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Background: The RAISE trial (NCT01183780) demonstrated that RAM plus FOLFIRI (leucovorin, fluorouracil, and irinotecan) significantly improved overall survival (OS) and progression-free survival (PFS) compared with placebo plus FOLFIRI (PBO) as second-line mCRC treatment. Despite multiple approved anticancer treatments targeting angiogenesis, there are currently no predictive markers to guide patient selection. The extensive RAISE biomarker program assessed the association of multiple candidate biomarkers with RAM efficacy outcomes.

Methods: Plasma and tumor tissue collection was mandatory in the RAISE trial. Analyses were performed using exploratory assays to assess the correlations of the baseline marker levels (vascular endothelial growth factor [VEGF]-C and D; soluble vascular endothelial growth factor receptor [sVEGFR]1, 2, and 3; and VEGFR2 immunohistochemistry in tumor tissue) with clinical outcomes. Cox regression analyses adjusted for stratification factors were performed for each marker.

Results: Biomarker results were available from >80% of patients. Among the candidate biomarkers analyzed, only VEGF-D levels had a consistent and statistically significant association with OS and PFS, suggesting a predictive relationship. Higher levels were associated with improved RAM efficacy (Table). This relationship was consistent across the full range of VEGF-D levels.

Conclusions: These analyses from RAISE identified VEGF-D as a potential predictive marker for RAM efficacy in mCRC. Further investigation of this relationship is being pursued.

Clinical trial identification: NCT01183780

Table: 555P Correlation of VEGF-D with Efficacy Outcomes: based on cut point from exploratory subset. Results below from combined exploratory + confirmatory groups

	OS				PFS			
Prespecified cut point	**≥115 pg/mL**		**<115 pg/mL**		**≥115 pg/mL**		**<115 pg/mL**	
Patients	RAM N = 270	PBO N = 266	RAM N = 176	PBO N = 172	RAM N = 270	PBO N = 266	RAM N = 176	PBO N = 172
Median (months) (95% CI)	13.9 (12.5, 15.6)	11.5 (10.1, 12.4)	12.6 (10.7, 14.0)	13.1 (11.8, 17.0)	6.0 (5.6, 7.0)	4.2 (4.1, 4.5)	5.4 (4.2, 5.8)	5.6 (5.3, 6.9)
HR (95% CI)	0.73 (0.60, 0.89)		1.32 (1.02, 1.70)		0.62 (0.52, 0.74)		1.16 (0.93, 1.45)	
p-value	0.0022		0.0344		<0.0001		0.1930	

Legal entity responsible for the study: Eli Lilly and Company

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556P A novel CpG panel is independently associated with colorectal cancer survival

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Background: Results of previous studies on the association of the CpG island methylator phenotype (CIMP) with colorectal cancer (CRC) prognosis were inconsistent and the variety of markers selected to define CIMP was widely blamed for the inconsistency. The current study was therefore aimed to comprehensively investigate the associations of DNA methylation at CIMP-related genes with CRC survival.

Methods: Patients with CRC diagnosed between 2003 and 2007 were followed up for a median of 5.2 years and divided into a screening cohort (n = 568) and a validation cohort (n = 308). DNA methylation was measured in tumor tissue using the Illumina Infinium HumanMethylation450 BeadChip. Cox proportional hazard regression models were used to estimate adjusted hazard ratios (HR) and 95% confidence intervals (CI) of survival after CRC, including adjustment for tumor stage, microsatellite instability, BRAF mutation status and other important factors.

Results: Of 48 genes used to define CIMP in the previous studies, 43 were also covered by the methylation array. In the screening cohort, ten CpG sites were identified to be associated with CRC survival. Seven of these ten CpG sites were also associated with CRC survival in the validation cohort and were used to construct a prognostic score. CRC patients with a prognostic score in the lowest tertile (lowest methylation levels at the CpG sites) showed poorer disease-specific survival compared with patients in the highest tertile in both the study cohort and the validation cohort (HR = 3.11; 95% CI = 1.97-4.91 and HR = 3.06; 95% CI = 1.71-5.45 respectively).

Conclusions: A CpG panel consisting of seven CpG sites was found to be strongly associated with CRC survival, independent from important clinical factors and mutations associated with CIMP.

Legal entity responsible for the study: Division of Clinical Epidemiology and Aging Research, German Cancer Research Center

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Disclosure: All authors have declared no conflicts of interest.

557P Predictive factors for early progression during induction chemotherapy (IC) and chemotherapy-free interval (CFI): Analysis from PRODIGE 9 trial

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Background: Some patients (pts) with mCRC have an early progression during induction chemotherapy (IC). Early identification of these pts is an important challenge in order to intensified front line treatment. For pts who have a tumor response or stabilization after IC a chemotherapy-free interval (CFI) could be proposed. Identification of the subgroup of pts that should not stopped chemotherapy (CT) and pts that will benefit from a long CFI is also of importance.

Methods: PRODIGE 9 pts had 12 courses of FOLFIRI + bevacizumab before an IC with or without bevacizumab monotherapy. As the pts are randomized before IC the whole strategy could be assessed. Following factors were evaluated for early progression during IC and for early (< 3 mths) or late progression (≥ 5 mths) during 1st CFI: treatment arm, sex, age, WHO PS, primary tumor resected, number of metastatic site, primary localization, leucocyte, platelets, alkaline phosphatase, CEA level, *KRAS* mutation, *BRAF* mutation and decrease of CEA at 2 months. Tumor response at the end of IC and early shrinkage at 1st evaluation were evaluated only for CFI duration. A logistic model was used to identify the prognostic factors with a . A significance level of 0.2 was required to enter into the model and to stay in the model.

Results: An early progression during IC occurred in 85 pts. Leucocytes $>10 \times 10^9$/L ($p = 0.02$), and decrease of less than 50% of CEA at 2 mths ($p = 0.01$) were associated with early progression. A first CFI was done in 344 pts. 128 pts had a short CFI, 100 an intermediate one between 3 and 5 mths and 116 a long CFI. Two factors were significantly associated with a short CFI: normal CEA at baseline ($p = 0.03$) and complete or partial response at 1st evaluation ($p = 0.08$). In the sub-group of 95 pts with *BRAF* determination, these 2 results were the same.

Conclusions: High baseline leucocytes count and the lack of decrease of CEA at 1st evaluation are associated with early progression and could be considered in favor of an early CT intensification. Two factors predict significantly CFI duration: Baseline CEA and tumor response to 1st evaluation. Surprisingly, our results suggest that a high baseline CEA and a stable disease at 1st evaluation are associated with a longer CFI.

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Legal entity responsible for the study: FFCD

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558P High PD-L1 expression and high CD8+ T-cell infiltration identifies a new subpopulation of colorectal cancer with high risk of relapse and poor outcome

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Background: CD8+ T-cell primary tumor infiltration is associated with improved colorectal cancer (CRC) outcome. However, the interaction between CD8+ T-cell infiltration and intra-tumor PD-L1 expression has not been previously characterized. This study aims to explore the impact of PD-L1 expression and degree of CD8+ T-cell infiltration on the outcome of patients with stage II and III CRC.

Methods: CD8, PD-1, PD-L1, cytokeratin 20, and CD68 expression were quantified via multi-spectral immunohistochemistry of primary CRC tumors from 35 patients with recurrent disease (cases) and 36 patients without recurrence (controls). The TCGA (The Cancer Genome Atlas) and the NCBI-GEO (Gene Expression Omnibus) datasets of 385 and 828 stage II-III cases, respectively, were used to validate the prognostic value of the discovery set biomarkers, both for relapse free survival (RFS) and overall survival (OS).

Results: In the 71-patient discovery case-control set, densities of CD8+ and PD-L1+ cells in tumor microenvironment classified patients into three distinct populations. High CD8+ cell infiltration (above median) and high PD-L1 expression (>90 percentile) was associated with high risk of relapse: all 7/7 patients with $CD8^{Hi}$/$PD\text{-}L1^{Hi}$ experienced disease relapse, despite being enriched in mismatch repair deficiency (4 patients). Low CD8+ cell infiltration was associated with a high relapse rate irrespective of PD-L1 status: 80% of patients with $CD8^{L}$ relapsed. $CD8^{Hi}$ in the absence of high PD-L1 expression ($CD8^{Hi}$/$PD\text{-}L1^{L}$) had the lowest risk of relapse: 7% of patients relapsed. The validation data sets confirmed that the $CD8^{Hi}$/$PD\text{-}L1^{L}$ and the $CD8^{L}$ groups carried an inferior RFS (NCBI-GEO data set: HR = 1.655, p = 0.02) and OS (TCGA data set: HR = 3.556, p = 0.0095) in comparison to the $CD8^{Hi}$/$PD\text{-}L1^{L}$ group. A multivariate analysis that includes age, stage, and mismatch repair (MMR) status, confirmed the independent impact of both $CD8^{Hi}$ and $PD\text{-}L1^{Hi}$ on RFS and OS in both validation sets.

Conclusions: $CD8^{Hi}$/$PD\text{-}L1^{Hi}$ defines 10% of patients with stage II/III CRC and confers a high risk of relapse, despite enrichment with MMR deficiency. This subgroup of patients may be suitable for the investigation of PD-1 checkpoint inhibitors.

Legal entity responsible for the study: City of Hope

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559P Clinical impact of molecular positive lymph node status in colorectal cancer

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Background: Accurate evaluation of lymph node (LN) status is important for prediction of prognosis and decision of postoperative adjuvant therapy in cancer patients. Histopathological diagnosis, usually used for this evaluation, has shortcoming of lower sensitivity due to observing only small portion of whole lymph node. To overcome it we developed a new molecular diagnostic system, one-step nucleic acid amplification (OSNA^{TM}) assay which measures cytokeratin (CK) 19 mRNA expression level in whole lymph node and reported the usefulness in colorectal cancer (CRC) as well as in breast, gastric and lung cancers. According to our recent study in CRC, 17.6% of stage II (histologically node negative) patients were found to be molecularly positive in OSNA assay. In this multicenter trial, we investigated the clinical impact of OSNA positive cases.

Methods: Patients with cN0 and cN1 CRC in 11 Japanese representative medical institutes were enrolled. All LNs were examined histopathologically by using one-slice hematoxylin-eosin staining. In addition, half of the LN, which could be cut into half (average, 9.8 LN/patient), was examined by OSNA assay. Patients were classified in accordance with the UICC staging criteria and OSNA results, and the 3-year disease-free survival (DFS) of each cohort was analyzed.

Results: We enrolled 204 patients with CRC, excluded 9 patients, and analyzed 195 patients (stage I: n = 50, stage II: n = 71, stage III: n = 74). Of the patients with node-negative CRCs, only one was OSNA positive at stage I, and 11 were OSNA positive at stage II. OSNA-positive stage II cases had much lower 3-year DFS rate than OSNA negative ones (p = 0.005). Among various clinical and pathological parameters, only OSNA status was a significant prognostic factor for 3-year DFS in stage II CRC cases (p = 0.025).

Conclusions: This prospective multicenter study showed for the first time a prognostic value of OSNA positivity in stage II CRC. This assay is useful for selecting high-risk patients with stage II CRC. Further study to determine the treatment strategy for patients with OSNA-positive stage II CRC is necessary.

Legal entity responsible for the study: OICI

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560P Impact of Immune response-associated gene polymorphisms on tumor response in rectal cancer patients treated with capecitabine +/- oxaliplatine and radiation in the ACCORD-12/PRODIGE-2 phase III trial

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Background: We examined whether 133 germline polymorphisms (SNPs) in 15 candidate genes *(CSF1R, IL8RA, TLR4, IL10, IL10RA, CTLA4, IL2, IL2RA, TGFb1, ICOS, IL13, IL13RA2, IFNgR, IL15* and IL15RA) would predict clinical outcome in the ACCORD-12 phase III trial which randomly compared neoadjuvant radiotherapy (RT) plus capecitabine (CAP45) with dose-intensified RT plus capecitabine and oxaliplatin (CAPOX50) in T3-4 Nx M0 resectable rectal cancer.

Methods: A candidate-gene association study was conducted in 316 patients (n = 161 in the CAPOX50 and n = 155 in the CAP45 arm). The primary end-point was tumor response according to the Dworak score in each arm. Logistic regressions were used to assess uni/multivariate associations. The Storey and Tibshirani method based on the control of false discovery rate was used (q-value <0.10 considered as true discovery). Multivariate models adjusted on treatment arm were performed to determine prognostic and predictive values of haplotypes (R package SNSassoc and function haplo.glm were used) for tumor response.

Results: In univariate analysis, two SNPs in IL2RA (rs11256456: OR = 5.1 [2.38; 11] and rs706781: OR = 4.2 [1.98; 8.74]) were significantly associated with the Dworak score in the CAP45 arm, and one in IL2RA the CAPOX50 arm (rs2104286: OR = 0.11 [0.01; 0.90]. All were confirmed in the multivariate analysis. Patients were categorized into 3 haplotype groups after the haplotype analysis of IL2RA rs11256456 and rs706781: one had a positive prognostic effect on tumor response in the CAP-45 arm (OR = 3.85 [1.97; 7.53], p = 0.0001) and in the overall population (OR = 1.76 [1.15; 2.68], p = 0.009). Interaction was also significant, suggesting a predictive positive effect of the same haplotype for response to CAP-45 (OR = 4.12 [1.71, 9.94], p = 0.002). None of the three IL2RA SNPs were correlated with survival in the multivariate analysis.

Conclusions: This pharmacogenetic analysis shows that SNPs in IL2RA are significantly associated with response to neoadjuvant chemoRT in patients with locally advanced rectal cancer. Their predictive effect may identify patients who benefit from CAP-45.

Legal entity responsible for the study: UNICANCER

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561P Improving treatment decisions in colon cancer: The tumor-stroma ratio (TSR) additional to the TNM classification

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Background: The tumor-micro-environment is an important determinant of tumor behaviour. We developed a new, easy to apply, practice changing method to select

colon cancer patients for adjuvant therapy: the tumor-stroma ratio (TSR). This parameter is independently validated. The current proposal aims to prepare implementation of the method by training international pathologists and prospective validation of the parameter in an international setting.

Methods: 1. A reproducibility study on TSR scoring in H&E stained tumor tissues will be conducted among international pathologists. An e-learning module will be developed with a quality assessment program in the framework of the European Society of Pathology EQA program. 2. Automation of the TSR using whole slide imaging and state-of-the-art pattern recognition techniques. 3. A prospective clinical trial will be performed that evaluates the introduction of the TSR in clinical practice.

Results: A high amount of stroma within the primary tumor results in worse patient outcome. The TSR can be determined at routine pathology diagnostics and has an excellent inter-observer agreement with $K > 0.80$. The TSR has been validated by independent international groups. Moreover it has been validated for breast, oesophageal, cervical, lung and gastric cancer. For colon cancer several cohort studies resulted in significant differences in survival time between stroma-high and stroma-low patients ($p < 0.0001$, HZ 2.5). These results were validated in the VICTOR trial (stage II, III: OS $p < 0.0001$, HR = 1.96; DFS $P < 0.0001$, HR = 2.15) and the Quasar II study (stage II, III: OS $p = 0.003$, HR = 1.53; DFS $p = 0.001$, HR = 1.53).

Conclusions: Standardization and prospective validation of TSR will result in inclusion of the parameter in the TNM classification leading to more accurate decision making for adjuvant chemotherapy.

Legal entity responsible for the study: Leiden University Medical Center

Funding: Dutch Cancer Society (KWF)

Disclosure: All authors have declared no conflicts of interest.

562P Development and validation of multiplex biomarker assay to stratify colorectal cancer (CRC) patient samples into subtypes

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Background: We previously classified colorectal cancer (CRC) into five distinctive subtypes (CRCAssigner) and later into four consensus molecular subtypes (CMS) based on microarray or RNAseq gene expression profiles. The goal of this study was to develop a less expensive multiplex biomarker assay to stratify patient samples into CRC subtypes using the nCounter platform (NanoString Technologies) with short turnaround time for potential clinical use.

Methods: We used three cohorts of primary untreated CRC samples (n = 51) with two microarray (Del Rio; Montpellier Cancer Research Institute, France and OriGene; OriGene, Rockville, MD, USA) and one RNAseq (SG; Singapore General Hospital, Singapore) gene expression profiles. We reduced our published 786-gene CRCAssigner signature (CRCAssigner-786) into a short gene panel (CRC-panel). Initially, we compared CMS subtypes with CRCAssigner-786 subtypes, followed by CRCAssigner-786 subtypes with that of the microarray/RNAseq-based CRC-panel. We then developed a customized nCounter CRC-panel and compared to different subtype classifications. To assess reproducibility, we generated technical replicates.

Results: There was an average of 70% concordance between CMS and CRCAssigner subtypes across different cohorts. 94% of predicted subtypes were concordant using microarray CRCAssigner-786 versus microarray CRC-panel signatures in both the Del Rio (16/17) and OriGene (16/17) cohorts. nCounter CRC-panel assay classified 82% (14/17) Del Rio and 65% (11/17) OriGene samples consistently with microarray-based CRC-panel classification. In the SG cohort, nCounter CRC-panel classified 76% (13/17) and 94% (16/17) of samples consistently with RNAseq-786 and RNAseq CRC-panel, respectively. Pearson's correlation coefficient between five pairs of technical replicates was 0.98.

Conclusions: nCounter assay stratified CRC samples into subtypes to known classifications. Given the high reproducibility and reduced costs, nCounter platform has been tested in formalin-fixed paraffin-embedded samples (ESMO-2017 Abstract-#3467). This assay may facilitate prospective validation of CRC subtypes in the clinic.

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563P HER2 overexpression and amplification in patients with colorectal cancer (HOLIC): A large-scale retrospective study in Chinese population

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Background: HER2 overexpression or amplification may be a potentially predictive factor for anti-HER2 response and anti-EGFR resistance in colorectal cancer (CRC). However, the prevalence of HER2 positivity in CRC patients and its correlation with clinicopathologic features are not clear.

Methods: HER2 and MMR protein expression were tested by immunohistochemistry (IHC) in formalin-fixed, paraffin-embedded samples from 4,913 consecutive CRC patients treated with surgical resection during 2011-2014 in our institution. Dual color silver-enhanced in situ hybridization (DISH) was performed in all IHC 3+/2+ cases. The scoring criteria of HER2 status in gastric cancer was used. RAS/BRAF mutation status was assessed by Sanger DNA sequencing.

Results: HER2 positivity was found in 160/4,913 (3.3%) cases, including 68 cases (42.5%) with IHC 3+ and 92 cases (57.5%) with IHC 2+/DISH+. HER2 positivity was more common in younger patients (<60 year old), correlated with perineural invasion, vascular invasion, lymph node metastases, and higher TNM stage. HER2 positivity was not related to tumor location. Only one HER2 positive case had MMR protein deficiency. Among the 160 HER2 positive cases, 56 (35%) harbored a KRAS mutation, 17 (10.6%) harbored a NRAS mutation, and 4 (2.5%) harbored a BRAF mutation.

Conclusions: To our knowledge, this is the largest study of HER2 status in Asian patients with CRC. HER2 positivity occurred in a small number of patients with CRC, related to unfavorable prognostic factors, more common in younger patients and rare in MMR deficiency cases. Compared with previous results in western population, the RAS/BRAF mutation rate of HER2 positive Chinese CRC patients seems much higher. The further study regarding molecular information of these HER2 positive CRC patients is ongoing.

Legal entity responsible for the study: Fudan University Shanghai Cancer Center

Funding: None

Disclosure: All authors have declared no conflicts of interest.

564P The inflamed immune phenotype can be induced by systemic treatment in angiogenic colorectal liver metastases in contrast to non-angiogenic liver metastases

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Background: Recent data suggest that patients with colorectal cancer who present with desmoplastic (angiogenic) histopathological growth pattern (HGP) colorectal liver metastases (CLM) might derive more benefit from bevacizumab-based chemotherapy than patients who present with replacement (non-angiogenic) HGP CLM.

Methods: The immune phenotype ('inflamed', 'excluded', 'desert') was analyzed regarding the association with HGPs in a cohort of 118 patients with resectable CLM [m:f 66:52, median age 62.3 (31.0-80.4) years, median follow-up 32.2 (5.0-92.7) months] treated with 3 months of neoadjuvant and adjuvant bevacizumab-based chemotherapy and liver resection. The HGPs of CLM were assessed on H&E-stained sections according to international guidelines. The immune phenotypes were based on the distribution pattern of cytotoxic T-lymphocytes in CD8-immunostained tissue sections.

Results: In 39.8% of the lesions the predominant means of vascularization was vessel co-option, as reflected by the replacement HGP. This non-angiogenic growth was associated with worse recurrence-free and overall survival (RFS, OS) with hazard ratios (HR) of 2.03 and 2.63 ($P = 0.002$ and $P = 0.005$, respectively). The HGPs were associated with the immune phenotypes. About 60% of the desmoplastic (angiogenic) HGP CLM were 'inflamed', while this was true for only 17% of the replacement (non-angiogenic) HGP CLM. More than half of the CLM with non-angiogenic growth were characterized by an immune desert as opposed to only 6% of the angiogenic CLM ($P < 0.001$). The non-inflamed immune phenotypes were associated with worse RFS (HR 1.85; $P = 0.03$).

Conclusions: Immune regulatory and angiogenesis pathways are known to interact. Our data suggest that the inflamed immune phenotype can be induced by systemic treatment in angiogenic CLM. The HGPs therefore are a potential biomarker for treatment that includes targeting the immune contexture.

Legal entity responsible for the study: Heinz-Josef Lenz

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Genentech/Roche, Merck, Gilead, Medimmune, Array, BostonMedical. All other authors have declared no conflicts of interest.

565P Whole-exome sequencing of matched germline and plasma cell-free DNA portrays the somatic mutation landscape of refractory metastatic colorectal cancer and identifies mutated KDR/VEGFR2 as new cause of therapy resistance

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Background: Anti-angiogenic therapies have been broadly used in oncology as in treatment of metastatic colorectal cancer (mCRC) patients, however the causes of resistance occurring in the majority of the patients treated remain largely unknown.

Methods: Whole-exome sequencing libraries of matched leukocyte and basal cfDNA samples (WES-gcfDNA) were generated and sequenced on HiSeq4000. *KDR*/VEGFR2 mutations were cloned and stably expressing CRC cell lines used for xenograft studies. Biochemical kinase assays were carried out to assess the impact of the VEGFR2 mutants on the inhibition of VEGFR2 kinase activity by cabozantinib, lenvatinib, axitinib and dovitinib. Patient-derived Avatar model was treated with multiple anti-angiogenic drugs. Somatic mutation landscapes depicted by WES-gcfDNA and the standard tumor WES (obtained later on) were compared.

Results: We investigated a RAS/BRAF/PIK3CA wild-type mCRC patient highly refractory to (sequentially): FOLFIRI-cetuximab; FOLFOX-bevacizumab; afatinib-cetuximab (phase-1 trial); oncolytic adenovirus monotherapy (phase-1 trial); capecitabine-bevacizumab; and finally regorafenib. No radiological or clinical benefit was observed after any of these treatments and the patient died due to his progressive disease within 14 months. WES-gcfDNA enabled us to identify the KDR/VEGFR2 L840F mutation exclusively in the cancer sample. Using the methods described above we obtained comprehensive experimental data showing that L840F decreases efficiency of TKIs, promote tumor growth and confer strong in vivo resistance to numerous anti-angiogenic therapies, including bevacizumab and VEGFR2 inhibitors. Other KDR/VEGFR2 somatic mutations we retrieved from cancer sequencing projects showed similar oncogenic and resistant phenotype.

Conclusions: Our study introduces WES-gcfDNA as a robust noninvasive gene discovery platform capable of portraying the somatic mutation landscape of metastatic cancer patients from blood sample solely. Moreover, we characterize a previously unexplored oncogenic and cancer therapy modulating role of VEGFR2 mutants.

Legal entity responsible for the study: Rodrigo Toledo, Manuel Hidalgo

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Disclosure: All authors have declared no conflicts of interest.

566P The nationwide cancer genome screening project in Japan, SCRUM-Japan GI-SCREEN: Efficient identification of cancer genome alterations in advanced colorectal cancer

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Background: We initiated the Nationwide Cancer Genome Screening Project in Japan since February 2014. From February 2015, we have introduced the Next Generation Sequencing to detect cancer genome alterations in advanced colorectal cancer (aCRC), 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 with corresponding targeting agents.

Methods: This study is ongoing with 20 major cancer centers. Patients with aCRC 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 October 31st in 2016, total of 1011 aCRC patients were enrolled and 981 samples were analyzed. The sequence was successfully performed in 751 tumors (76.6%). Out of 751 patients, the origin of samples included the primary site of 83.1% (Right-side 24.6%, Left-side 58.5%), metastatic site of 15.3%, and unknown of 1.6%. The frequently detected mutations in 751 samples of which results were available were TP53 (69.0%), APC (62.8%), and KRAS (43.8%), and CNVs ($\geq$ 7copies) were FLT3 (3.6%), ERBB2 (2.8%), and MYC (2.7%). BRAF V600E was identified in 48 cases (6.4%) and CCDC6-RET fusion was identified in one case (0.1%). 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 aCRC. This novel knowledge provides an intriguing background to investigate new targeted approaches in these patients and represents the progress toward precision medicine.

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567P Clinical utility of quasi-monomorphic variation range (QMVR) on the determination of microsatellite instability (MSI) status in patients (pts) with colorectal cancer (CRC): GI-SCREEN-CRC-MSI sub-study 01

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Background: The current analysis for the determination of Microsatellite Instability (MSI) status in tumors requires matched normal DNA as references. Five quasi-monomorphic markers (NR-21, BAT-26, BAT-25, NR-24, and MONO-27) of the Promega panel are known to have few variant alleles in both Caucasian and Asian patients (pts). For that reason, the peak of PCR products from normal DNA are confined within the Quasi-Monomorphic Variation Range (QMVR), of which Japanese pts with metastatic colorectal cancer (mCRC) are almost the same as those of Caucasian (Patil DT, et al., 2012 and Bando H. ASCO-GI 2017).

Methods: The purposes of this clinical evaluation study are to establish the QMVR in Japanese pts with mCRC and to evaluate the clinical utility of the QMVR in the determination of MSI status without matched normal DNA. The primary endpoint is the concordance of MSI status between the standard method using DNA from tumor plus matched normal samples and testing method using DNA from only tumor samples.

The new MSI kits including the Promega MSI panel were manufactured under the Quality Management System (QMS) for *in vitro* diagnostics (IVDs). As the decision algorithm, tumors exhibiting 2 or more markers outside the QMVR were classified as MSI-H, cases with 1 marker or without any marker outside the QMVR were classified as non MSI-H (MSI-L/MSS).

Results: Totally 435 pts with mCRC were enrolled. Median age was 66 years old and 248 (57.0%) pts were male. 368 (84.6%) primary and 67 (15.4%) metastatic specimens were used. There were 11 (2.5%) MSI-H cases by the standard method and the sensitivity of the testing method was 100% while the specificity of the testing method was also 100%. Thereby the two methods was completely concordant. Among the five quasi-monomorphic markers, 3 and 2 cases were discordant in NR-21 and BAT-25, respectively. In BAT-26, NR-24, and MONO-27, all cases were completely concordant.

Conclusions: By using the QMVR, MSI status of Japanese pts with mCRC can be determined without matched normal DNA, and the QMVR might be applicable to Caucasian pts.

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568P The impact of antithrombotics on immunochemical fecal occult blood testing for colorectal cancer screening

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Background: The impact of antithrombotics on immunochemical fecal occult blood testing (iFOBT) for colorectal cancer (CRC) screening in the general population remains unclear.

Methods: A prospective cohort of patients undergoing endoscopy for positive iFOBT in 2015 at 3 centers in Belgium was analyzed. Medical records were reviewed for demographic and clinical variables: gastro-intestinal (GI) symptoms, family history of polyps/CRC, use of antithrombotics (including Aspirin and/or Clopidogrel, Dipyridamole, Ticagrelor, novel anticoagulants or vitamin K antagonists). Endoscopy reports were checked for colorectal pathology. Significant findings were defined as CRC or advanced adenomas. Rates of false positive iFOBT and detection of CRC or advanced adenomas were compared in patients with and without antithrombotics or Aspirin. Finally a distinction was made between patients who had a iFOBT through programmatic or opportunistic screening.

Results: A total of 510 patients (64% male, median (IQR) age 63.2 years) with positive iFOBT were included. Colorectal pathology was confirmed in 73% of the patients; more commonly in males and family history. Significant findings were present in 220/371 (59%) patients with colorectal pathology. Antithrombotics were used in 25% of the patients and associated with male gender, older age and lower GI symptoms. Aspirin alone was used in 17% and associated with male gender and older age. Rates of false positive iFOBT, detection of advanced adenoma and CRC were similar in patients with or without antithrombotics and in patients with Aspirin alone compared to no antithrombotics. iFOBT was mainly used in programmatic screening (91%), with no differences in demographic or clinical variables between these two groups.

Conclusions: Although antithrombotic drugs were mostly prescribed in male and older patients with an inherent higher cancer risk, detection rates of CRC and advanced adenoma's were similar. Despite the higher rate of lower GI symptoms, antithrombotics or Aspirin alone did not lead to more false positive iFOBT. Use of antithrombotics or Aspirin alone does not seem to impact the performance of iFOBT for screening of CRC in the general population.

Legal entity responsible for the study: OLV Aalst

Funding: None

Disclosure: All authors have declared no conflicts of interest.

569P miR-93 regulates epithelial-to-mesenchymal transition process in metastatic colorectal cancer by targeting EphA4

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Background: Regulating epithelial-to-mesenchymal transition (EMT) in cancer cells has been widely considered as an approach to combat cancer progression and therapeutic resistance, whereas a limited number of broadly comprehensive investigations of microRNAs involved in metastatic colorectal cancer (mCRC) have been conducted. In this study, we investigated the roles and mechanisms of EMT process in mCRC.

Methods: We used in situ hybridization and quantitative reverse transcriptase polymerase chain reaction to measure expression of miR-93 in colorectal tissues, nontumor tissues and metastatic liver tissues. CRC cell lines were transduced with lentiviruses that expressed miR-93, its inhibitor sequence targeted miR-93 or a scrambled sequence (control); proliferation, metastasis, invasion and colony formation were analysed. We analysed growth of CRC cells that overexpress miR-93 or its inhibitor in severe combined immune-deficient mice. Western blot, and luciferase reporter assays were used to measure expression and activity of Eph tyrosine kinase receptor (EphA4) and related signalling molecules.

Results: In this study, we demonstrated that miR-93 regulated the epithelial-mesenchymal transition (EMT) process by targeting EphA4 in metastasis colorectal cancer (mCRC). We examined the fact that CRC tissues and metastatic liver tissues had increased levels of miR-93 compared with the nontumor tissues and cells, by which we identified miR-93 can regulate EMT process. In addition, overexpression of miR-93 increased proliferation of CRC cells, metastasis, invasion and colony formation in vitro, whereas miR-93 depletion reduced these parameters. In severe combined immune-deficient mice, overexpression of miR-93 by CRC cells increased liver metastasis and overexpression of the miR-93 inhibitor reduced it. By further study the role of miR-93 in EMT and tumor metastasis, we identified by microarray analysis that the direct and functional target genes of miR-93 was EphA4. Knockdown of EphA4 phenocopied the effect of miR-93 and ectopic expression of EphA4 restored the effect of miR-93 on proliferation, migration, invasion and liver metastasis in CRC cells.

Conclusions: Our findings for the first time revealed that miR-93 regulates the epithelial-mesenchymal transition (EMT) process by targeting EphA4 to affect liver metastasis in colorectal cancer (CRC). Mechanistically, miR-93 inhibited tumor metastasis by directly targeting EphA4 which is a crucial factor in regulating EMT. Collectively, this study provide new insights into exploring the therapeutic potential of miR-93 which is able to regulate EMT process to affect tumor metastasis, and warrant further study in clinical settings.

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Legal entity responsible for the study: Department of Colorectal Cancer, Shanxi Cancer Hospital and Institute

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Disclosure: All authors have declared no conflicts of interest.

570P Array based profiling of emerging molecules in colorectal cancer

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Background: Colorectal cancer (CRC) also has various genetic backgrounds and diversity. In addition to the RAS gene, a lot of new knowledge about molecules playing an important role in the process of carcinogenesis or drug resistance, and emerging molecules as targets for new treatments have been reported recently. In this research, we aim to clarify correlation between emerging molecules and differences through clinical stages in CRC usig tissue array.

Methods: Consecutive patients who underwent sugery in our hospital from June 2003 to March 2011 were enrolled in this study. Tissue array based profiling of emerging molecules was performed on archival samples using immunohistochemistry for MLH1/MSH2/MSH6/PMS2, CDX2, HER2 and PD-L1, and fluorescence in situ hybridization for *ERBB2*. We analyzed the correlation among molecular profile, overall survival, pathological findings and location of CRC.

Results: A total of 1122 CRC from stage 0 to IV were analyzed; details in Table. In dMMR population, the proportion of PD-L1 expression (19.2%) was increased significantly compared to those in pMMR population (2.5%). In the univariate analysis, CDX2 negative, BRAF mutation and poorly differentiated histology and in the multivariate analysis, CDX2 negative, dMMR and poorly differentiated histology were idnetified as predictive factors for OS in whole population.

Conclusions: Our data comprehensively summarized the significance of the recent emerging molecules in CRC over the clinical stages. These are considered to contribute to precision medicince in near future.

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Table: 570P

	All patients (n = 1122)
Median age (±SD)	65±11.5
Sex, n (%)	
−Male	586(52.2)
−Female	536(47.8)
Stage of disease at time of presentation, n (%)	
−0	26(2.3)
−I	215(19.1)
−II	318(28.3)
−III	348(30.9)
−IV	212(18.8)
−Unknown	3(0.2)
Pathology of primary tumor, n (%)	
−differentiated	1024(91.4)
−poorly differentiated	86(7.6)
−unknown	13(1.1)
Site of primary tumor, n (%)	
−Right sided	346(30.8)
−Left sided	757(7.6)
−Unknown	22(1.9)
Molecular status, n (%)	
−dMMR	78(6.9)
−CDX2 negative	43(3.8)
−BRAF V600E mutation by IHC	35(3.1)
−HER2 3+	34(3.0)
−ERBB2 amplification	26(2.2)
−HER2 3+ and ERBB2 amplification	23(2.0)
−PD-L1 positive	41(3.6)

571P Multiplatform assay to classify formalin-fixed paraffin-embedded (FFPE) colorectal cancer (CRC) samples into molecular subtypes with mutational profiles

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Background: The implementation of CRC subtypes along with other molecular features in clinic is challenging due to lack of easy-to-use and low cost assays suitable for FFPE tissues. Based on our CRCAssigner and Consensus Molecular Subtype (CMS), we validated a small gene panel for nCounter assay (Nanostring Technologies) to classify CRC fresh-frozen samples (ESMO 2017 Abstr 4633). Here, we tested nCounter and MiSeq platforms (Illumina; targeted mutational panel) in archival FFPE samples.

Methods: Tissues from 36 chemorefractory patients treated at the Royal Marsden were collected. Tumour-enriched areas were macrodissected, RNA/DNA was extracted, and nCounter assay was performed. RNA technical (same extraction, n = 6) and biological (same block, different extractions, n = 3) replicates were generated. Hotspot *BRAF*, *KRAS*, *NRAS*, *PIK3CA*, *TP53* mutations (MT) were sequenced.

Results: Out of 26 untreated primaries, 8 were enterocyte/transit-amplifying (TA) (CMS2, 30%), 7 goblet-like (CMS3, 27%), 8 stem-like (CMS4, 30%), 0 inflammatory (CMS1), and 3 mixed subtypes. *BRAF/RAS* MT were mutually exclusive and detected in all goblet-like (CMS3) samples. Interestingly, *PIK3CA* mutation was exclusively present in differentiated (goblet-like and enterocyte) subtypes, whereas *TP53* mutation was detected in all the subtypes. Among 10 pre-treated samples, 3 were inflammatory (CMS1, 30%), 3 TA (CMS2, 30%), 3 stem-like (CMS4, 30%), and 1 mixed subtypes. Pearson correlation coefficients were 0.96 and 0.88 (high reproducibility) for technical and biological replicates, respectively.

Conclusions: With the caveat of small numbers, the subtype distribution in chemorefractory patients is different compared to early stage patients assessed within the CMS consortium. The enrichment for less differentiated subtypes in pre-treated samples suggests potential treatment-induced changes in tumours. Overall, nCounter assay along with MiSeq platform was able to classify standard archival diagnostic CRC FFPE samples into subtypes, which warrants further improvement and validation for clinical practice.

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572P A robust gene signature for the detection of early relapse in stage I-III colon cancer

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Background: Almost 40% to 50% of colon cancer relapse emerged within the first year after initial primary resection. We hypothesized that differences in mRNA expression before treatment could identify patients at high risk of early relapse.

Methods: Public microarray datasets of stage I-III colon cancer samples were extracted from Gene Expression Omnibus database. Propensity score matching analysis was performed between patients in early relapse group and long-term survival group from GSE39582 discovery series (N = 386) and internal validation series (N = 111). Linear Models for Microarray data (LIMMA) method were then used to identify the differentially expressed genes (DEGs). We then built an eight-mRNA-signature using Cox regression model. Time-dependent ROC was used to analyze the predictive accuracy of this classifier in both the discovery and internal validation series. The prognostic value of the signature was further externally validated in GSE14333 and GSE33113 datasets.

Results: After DEGs analysis, eight mRNAs were found with more than 1.5 fold changes and P value <0.05 both in discovery and internal validation sets. With specific risk score formula, patients were further classified into high-risk group and low-risk group. Relapse free survival was significantly different between the two groups in every series including discovery, internal validation and another two external validation sets of patients. Time-dependent ROC at 1 year suggested the more prognostic accuracy of classifier (AUC=0.717) than AJCC TNM staging system (AUC=0.631) in the entire GSE39582 (N = 498) dataset.

Conclusions: We developed a robust mRNA signature consisting of both up- and down-regulated mRNAs that can effectively classify colon cancer patients into groups with low and high risks of early relapse. This mRNA signature may help select high-risk colon cancer patients who deserve more aggressive therapeutic intervention.

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Disclosure: All authors have declared no conflicts of interest.

573P microRNA(miR) subtypes correlates with colorectal cancer(CRC) molecular subtypes: Validation of miR-30b interaction with genes up-regulated in the high-stroma subtype

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Background: Colorectal Cancer (CRC) is a heterogeneous disease. Microarray molecular profiling has been used to identified tumor subtypes with different clinical behavior (1,2). Our main objective was to find out whether microRNAs (miR) were able to classify CRC tumors in the same way as mRNA and to identify miR targets in the colon tumors associated to the poor outcome High-stroma/CMS4 subtype.

Methods: mRNA and miR expression were analyzed in 88 colorectal tumors (24 Dukes A, 26 B, 19 C, 19 D) using gene expression and miR microarrays. Hierarchical clustering was used to classified tumors based on miR expression. Association or miR subtypes to mRNA subtypes and to CMS was carried out. TALASSO software (http://talasso.cnb.csic.es) was used to find miR-mRNA interactions. Candidate gene-miR interactions were scored and biologically validated in 293T cell line.

Results: Expression profiling of miRs revealed three molecular subtypes clearly associated with those obtained by mRNA expression profiling (p = 0.000 for HC subtypes

and p = 0.001 for CMS subtypes). miR subtype 1 associates with the Low-stroma/CMS2 Subtypes, miR subtype 2 correlates with the High-stroma/CMS4 subtypes and miR subtype 3 is associated with Mucinous-MSI/CMS1 subtypes. 788 genes showed significant interaction with 176 miRs ($p < 0.05$). Based on the biological relevance and the expression profile between subtypes, 88 miR-mRNA interactions were selected as candidates. SLC6A6 that is up-regulated in the high-stroma/CMS4 subtype, showed interaction with miR-30b (P = 0.035). Site-directed mutagenesis over the predicted region of interaction in SLC6A6 3'-end led to the loss of the interaction (p = 0.201).

Conclusions: 1. There is a clear correlation between mRNA classification and 3 novel miR subtypes. 2. miR subtype 1 is associated with Low-Stroma/CMS1 subtype, miR subtype 2 with High-stroma/CMS4 subtypes and miR subtype 3 with Mucinous-MSI/CMS1 subtypes. 3. High-stroma gene (SCL6A6) shows specific interaction with miR-30b.

Legal entity responsible for the study: Instituto de Investigación Sanitaria San Carlos, Hosptal Clínico San Carlos

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574P Gene expression changes in the immunotherapy targets CTLA4 and LAG3 in right- and left-sided colorectal cancer tissues during preoperative oral uracil and tegafur/leucovorin chemotherapy

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Background: Oral uracil and tegafur (UFT)/leucovorin (LV) are widely used as a standard adjuvant chemotherapy for colorectal cancer (CRC). On the other hand, immune checkpoint inhibitors such as pembrolizumab are being developed for the treatment of patients with CRC with high microsatellite instability or a mismatch repair deficiency. However, the effects of standard chemotherapy on the expression levels of immunotherapy targets are unknown. In the present study, we examined the gene expression levels of immunotherapy targets in tumor tissues before and after UFT/LV chemotherapy in patients with CRC.

Methods: The subjects were 80 patients with CRC who were scheduled to undergo surgery. UFT (300 mg/m^2/day) and LV (75 mg/day) were administered for 2 weeks before surgery. Using an RT-PCR assay, the gene expression levels of four immunotherapy targets, CD274, CTLA4, IDO1 and LAG3, were quantitatively evaluated in paired samples of tumor-biopsy specimens obtained before chemotherapy (pre-samples) and resected-tumor specimens obtained after chemotherapy (post-samples).

Results: In the pre-samples, no differences in the gene expression levels of the four immunotherapy targets were observed between the right- and left-sided colorectal cancer biopsy specimens, but the gene expression levels of LAG3 were significantly higher in elderly patients (≥75 years) than in younger patients (<75 years) ($P = 0.0027$). When the pre- and post-samples were compared, the gene expression levels of CTLA4 and LAG3 were significantly higher after UFT/LV chemotherapy ($P = 0.0003$ and $P = 0.0111$, respectively). Interestingly, these increases in gene expression were only observed in left-sided tumors ($P < 0.0001$ and $P = 0.0056$, respectively), and not in right-sided tumors ($P = 0.3922$ and $P = 0.4085$, respectively).

Conclusions: The increases in the gene expressions of the immunotherapy targets CTLA4 and LAG3 after oral chemotherapy with UFT/LV were specific to left-sided colorectal tumors, suggesting that immunotherapy strategies for patients with CRC after standard chemotherapy should be considered separately for right- and left-sided colorectal tumors.

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Disclosure: All authors have declared no conflicts of interest.

575P Prognostic value of microsatellite instability status in stage II/III rectal cancer patients who received upfront surgery

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Background: Microsatellite instability (MSI) is one of the most important prognostic factors in patients with colon cancer but the impact of MSI in rectal cancer, which is known to have a lower incidence of MSI-high (MSI-H) tumours than proximal colon cancer, has not been fully evaluated. We studied whether MSI status affects survival in stage II and III rectal cancer patients who underwent upfront curative resection.

Methods: 1138 patients who had operation between February 2008 and August 2015 in a single, tertiary care center in South Korea were included and PCR-based MSI testing was performed on tumour tissue from each patient. Study endpoints were disease free survival (DFS) and overall survival (OS).

Results: Among 1138 patients, 25 (2.2%) had MSI-H tumours. Compared with microsatellite stable (MSS) or MSI-low (MSI-L) tumours, MSI-H showed similar clinical characteristics including age at diagnosis, gender, tumour location and pathologic tumour stage but they were highly associated with histological grade of tumour (p = 0.005) and presence of family history of colorectal cancers (p = 0.003). The 5-year DFS rates for patients with MSI-H and MSS/MSI-L were 78.0% and 69.2%, respectively (p = 0.637), and the 5-year OS rate was 84.0% with MSI-H and 82.4% with MSS/MSI-L (p = 0.735). On multivariate Cox regression analysis, there was also no significant difference in either DFS (p = 0.855) or OS (p = 0.912) for the patients with rectal cancer based on MSI status.

Conclusions: Our results suggested that MSI has no definite prognostic role in patients with rectal cancer. MSI status was associated with differentiation of tumour and family history of colorectal cancer.

Legal entity responsible for the study: Department of Oncology, Asan Medical Center, Seoul, Republic of Korea

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Disclosure: All authors have declared no conflicts of interest.

576P Biomarker testing practices in the SECURE (proSpective obsErvational clinical practiCe stUdy in the first-line management of metastatic colorectal cancer [mCRC] with eRbitux in combination with chemothErapy) study

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Background: First-line treatment decisions in patients with mCRC are influenced by biomarker testing. The purpose of the SECURE study is to obtain real-world evidence regarding the decision pathway in first-line treatment selection. Here, we report information concerning biomarker testing practices in the SECURE study.

Methods: SECURE is a 2-part, noninterventional, multicenter, multinational, open-label, prospective phase 4 study being conducted in Algeria, Egypt, Greece, Iran, and Oman. In the first part of the study, patients with previously untreated mCRC were followed to record biomarker testing practices and first-line treatment decisions; treatment decisions were entirely at the discretion of the investigators. The second phase of the study – which is ongoing – involves monitoring clinical outcomes in patients with *RAS* wild-type mCRC treated with cetuximab-based regimens.

Results: Biomarker testing was performed in 169 of the 182 (92.9%) evaluable patients in the first phase of the SECURE study. *KRAS* (91.8%), *NRAS* (74.2%), *BRAF* (25.8%), and EGFR (20.9%) were the most commonly assayed biomarkers; also, microsatellite instability, PI3KCA, p53, PTEN, and MSH6 were measured in < 10% of patients. Biomarker testing was performed in-house in only 4.9% of cases, whereas 87.9% of biomarker testing occurred in external laboratories. Of interest, the median total duration of biomarker testing was < 10 days (*KRAS*, 9 days; *NRAS*, 9 days; *BRAF*, 8 days; EGFR, 8 days), and the median duration between biomarker testing results and the initiation of cetuximab-based therapy was 14 days. In our cohort, upon *KRAS* assessment, 47.3% of patients were found to be wild-type, 39.6% mutant, 1.6% inconclusive, 2.7% not available, and 0.5% missing. Updated data will be presented at congress.

Conclusions: SECURE provides clarity regarding the decision pathway for patients presenting with mCRC. Our findings suggest that biomarker testing occurs in the overwhelming majority of cases, although opportunities may exist to further optimize biomarker testing practices and better guide treatment decisions.

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577P Exosomal ECM1 protein expression in plasma from the tumor-draining vein (mesenteric vein) and time to relapse in colon cancer patients

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Background: Exosomes are microvesicles that contain and transport coding and non-coding RNA, DNA, and proteins. They are secreted by several cell types, including

tumor cells, and captured by receptor cells in a target organ, where they modify the tissue microenvironment, forming a pre-metastatic niche where circulating tumor cells can anchor. It has recently been found that blood from a tumor-draining vein can provide more reliable information about biomarkers than that obtained from a peripheral vein (PV). Venous return from the colon occurs through the mesenteric veins (MV), making the MV an excellent source to analyze potential biomarkers contained in exosomes released by the tumor cells in colon cancer before they reach the target organ. We have assessed the presence of exosomal proteins in the MV and PV of surgically resected colon cancer patients and correlated our findings with time to relapse (TTR).

Methods: On the day of surgery, blood samples were obtained from the MV and PV of 31 stage I-III colon cancer patients. Exosomes were isolated by ultracentrifugation and confirmed by cryogenic transmission electron microscopy. High-throughput proteomic analysis by mass spectrometry was used to identify expression levels of exosomal proteins. Findings were confirmed by western blot in MV and PV samples, as well as in samples from healthy controls, using TSG101 as a recognized marker of exosomes.

Results: TSG101 was more highly expressed in relapsed patients than in non-relapsed patients or controls. The ECM1 protein was more highly expressed in both MV and PV exosomes from patients than in those from controls. However, ECM1 expression was 13 times higher in relapsed than in non-relapsed patients in MV – but not PV – exosomes. Among 17 patients with low exosomal ECM1 levels in MV, TTR was 40.2 months, compared to 31.3 months for 14 patients with high levels ($P = 0.04$).

Conclusions: ECM1 and TSG101 are higher expressed in relapsed patients and high expression of exosomal ECM1 released by the tumor is associated with shorter TTR. The analysis of exosomes isolated from the tumor-draining vein, the MV, is a promising method for the identification of biomarkers before reaching the target organ.

Legal entity responsible for the study: University of Barcelona

Funding: University of Barcelona

Disclosure: All authors have declared no conflicts of interest.

578P LAG-3 expression in tumor infiltrating immune cells is associated with poor prognosis in patients with microsatellite instability high colon cancer

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Background: Recent findings demonstrated that microsatellite instability high (MSI-H) colon cancer contains high T-cell infiltration and highly upregulated expression of multiple immune checkpoints. There is increasing evidence on the role of LAG-3 in the downregulation of T cell responses and on its involvement in tumor-infiltrated T regulatory function. The aim of this study was to reveal the prognostic impact of MSI-H colon cancer showing immune checkpoint protein expressions, which are good candidates for immunotherapy.

Methods: From January 2011 to April 2015, we included 98 patients with MSI-H colon cancer who underwent curative surgery at Kyungpook National University Medical Center. Inhibitory receptors such as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), lymphocyte-activation gene 3 (LAG-3), programmed death-ligand 1 (PD-L1), programmed cell death 1 (PD-1) and indolamine 2'3'-dioxygenase (IDO) expression status were retrospectively analyzed using immunohistochemistry (IHC). Positivity in tumor cells (T) and immune cells (I) were separately evaluated. IHC values were determined to be positive when moderate or strong intensity of the membranous to cytoplasmic staining pattern were shown in more than 5% of the tumor cells or immune cells.

Results: Among the 93 patients, 22 patients (23.9%) and 63 (68.5%) were determined as PD-L1(T) positive and PD-L1 (I) positive, while 12 (13.2%) and 42 (45.7%) were determined as LAG-3(I) positive and PD-1 (I) positive. Twenty-seven patients (29.3%) and 66 (71.7%) were determined as CTLA-4 (T) positive and CTLA-4 (I) positive, while 66 (71.7%) and 26 (28.3%) were determined as IDO (T) and IDO (I) positive. During median follow-up duration of 39 months, 16 (17.4%) patients experienced recurrence. LAG-3 (I) positivity was significantly associated shorter relapse-free survival ($p = 0.016$). Moreover, LAG-3 expression was significantly correlated with PD-L1 (T) expression ($p = 0.003$). Co-expression of PD-L1 and LAG-3 showed worse prognosis for relapse-free survival ($p < 0.001$).

Conclusions: In conclusion, LAG-3 positivity showed worse prognosis in patients with MSI-H colon cancer.

Legal entity responsible for the study: Kyungpook National University Medical Center

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Disclosure: All authors have declared no conflicts of interest.

579P Primary efficacy results and clinical impact of UGT1A1 genotype on safety from a Phase II study of FOLFOXIRI plus bevacizumab in patients with metastatic colorectal cancer: The QUATTRO study

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Background: The TRIBE study showed that FOLFOXIRI plus bevacizumab (Bmab) significantly improved efficacy outcomes as first-line treatment in patients (pts) with metastatic colorectal cancer. A prospective single-arm, multicenter, phase II study investigated the efficacy and safety of Japanese pts.

Methods: Pts were treated with 12 cycles of FOLFOXIRI plus Bmab as induction therapy followed by maintenance with 5-FU plus Bmab until disease progression or unacceptable toxicities. Pts with the double heterozygous or homozygous genotype of the UGT1A1 *28 and *6 polymorphisms were excluded. Prophylactic uses of G-CSF were not permitted. The primary end point was progression-free survival (PFS) rate at 10 months by investigator, which was confirmed by central assessment.

Results: Totally, 69 pts were enrolled. The median age was 60 years, and 42 pts were male. 39 pts with the UGT1A1 single heterozygous genotype and 30 pts with wild-type were enrolled. At a median follow-up time of 19.6 months, the PFS rate at 10 months by investigator and central assessment were 75.2% (95% CI, 63.8–86.6) and 69.0% (95% CI, 56.6-81.4), respectively. The median PFS was 13.3 months (95% CI, 11.5–19.4). The response rate and the rate of early tumor shrinkage were respectively 73.9% and 71.0%, achieving R0 resection rate of 24.6%. The major grade ≥ 3 adverse events were neutropenia (74%), hypertension (35%), and febrile neutropenia (FN; 22%). One treatment-related death occurred. During the first 2 cycles of induction therapy, grade 4 neutropenia and FN in UGT1A1 single heterozygous pts were 46% and 26%, while those in wild-type pts were 13% and 10% ($P = 0.0044$ and $P = 0.127$). However, no association in terms of efficacy between UGT1A1 single heterozygous and wild-type pts was indicated.

Conclusions: The efficacy of FOLFOXIRI plus Bmab in Japanese were consistent with those of previous phase II and III studies, with manageable but different toxicity profiles in terms of grade 4 neutropenia and FN between UGT1A1 single heterozygous and wild-type pts. Prophylactic use of G-CSF in UGT1A1 single heterozygous pts was suggested considering the high incidence of grade 4 neutropenia and FN.

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Legal entity responsible for the study: EPS Corporation

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580P The expression of interleukin 17 receptor A is associated with poor prognosis in patients with colorectal cancer and its knockdown inhibits tumor growth and modulates tumor-infiltrating immune cells in mice tumor

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Background: Interleukin 17 receptor type A (IL17RA) is a potent mediator in the pathogenesis and progression of colorectal cancer. Our previous study has shown that IL17A is a potential therapeutic target in modulating tumorigenesis, and metastasis, and serves as a prognostic marker in colorectal cancer (CRC), but the role of IL17RA in colonic tumorigenesis is still not clear. This study aims to evaluate the potential role and function of IL17RA in CRC.

Methods: IL17RA expression was determined in colorectal cancer tissues and adjacent normal tissues of CRC patients by using quantitative RT-PCR and immunohistochemistry. To investigate the functional significance of IL17RA expression, and clinical significance of IL17RA expression in CRC patients, disease-free survival was analyzed in patients with CRC. The IL17RA knockdown stable clones were used for in vitro migration/invasion assay and were subcutaneously implanted in mice to measure tumor growth.

Results: A higher IL17RA mRNA level in tumor tissue of CRC patients than adjacent normal tissues ($p = 0.0016$) was found and it was significantly correlated with recurrence ($p = 0.008$) and poor disease-free survival ($P < 0.001$). The knockdown of IL-17RA affected the tumor microenvironment and decreased tumor volume of subcutaneous xenograft model. The scarcity of IL-17RA were found to inhibit the percentage of intratumoral tumor-infiltrating leukocytes including CD4+ CD25+ regulatory T cells and myeloid-derived suppressor cells as determined by flow cytometry analysis. Moreover, IL-17RA-knockdown cells increased apoptotic ability via upregulating PARP1, cleaved-caspase 3.

Conclusions: IL-17RA participates in mediating tumor growth and angiogenesis of CRC and plays a crucial role in the progression of CRC. It could serve as prognostic marker of CRC patients and could potentially be used as a therapeutic target in clinical application.

Legal entity responsible for the study: Chih-Yung Yang

Funding: None

Disclosure: All authors have declared no conflicts of interest.

582P Comparison of performances of three technologies for detection of RAS mutations in cfDNA (NGS strategy, BEAMing assay and ddPCR BioRAD assay)

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Background: A number of RAS mutations confer resistance to anti-EGFR treatments used in the management of colon cancer. The objective of this study was to evaluate the ability of cell-free plasma DNA (cfDNA) to reflect the mutational status of a tumor in order to use liquid biopsies instead of invasive and painful solid tumor biopsies when monitoring tumor progression.

Methods: We selected tumors from the CIRCAN_0 cohort. The molecular profiles from solid biopsies were routinely assessed with the PGM NGS technology. Plasma samples were collected at diagnosis (colon cancer) and during progression (lung cancer). KRAS and NRAS somatic alterations were quantified using three different technologies: droplet digital polymerase chain reaction (ddPCR) from BioRad and BEAMing (Oncobeam) from Sysmex Innostics, as well as next generation sequencing (NGS, NextSEQ500 by Illumina) using the library prepared with the 56G oncology panel kit from Swift Biosciences.

Results: The highly sensitive and specific assays enabled us to obtain excellent matches with solid biopsies determined in cfDNA for colon cancer at diagnosis and for lung cancer during disease progression. When examining cfDNA from patients displaying mutations in their colon biopsy for one of the KRAS and/or NRAS mutations, 100% of the mutations were confirmed using the OncoBEAM technology, whereas only 66% matched the initial PGM status using the two other technologies. The BEAMing technology enabled us to detect KRAS mutations in patients with negative biopsy, increasing the detection of the KRAS positive profiles compared to the standard solid biopsy method. cfDNA was sampled during progression and the high sensitivity and reproducibility of the BEAMing technology enabled us to identify patients with KRAS persistence and others, developing an additional mechanism of relapse.

Conclusions: The advantage of the NGS technology is the larger coverage of longer gene regions for screening purposes, while the BEAMing technology provides highly sensitive results allowing us to follow the kinetics of appearance and disappearance of somatic alterations, linked to the efficiency of therapies.

Legal entity responsible for the study: Hospices Civils of Lyon

Funding: AstraZeneca, Sysmex, Merck

Disclosure: All authors have declared no conflicts of interest.

583P Impact of tumor location on the efficacy of first-line anti-EGFR monoclonal antibody plus chemotherapy in patients (pts) with metastatic colorectal cancer (mCRC): Retrospective analyses of the randomized MACRO-2 and PLANET trials from TTD Group

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Background: mCRC is a group of heterogeneous diseases rather than a homogeneous one, resulting in clinical and molecular characteristics between right- and left-sided tumors driving to different prognosis.

Methods: Pts with KRAS Wild-Type (WT) mCRC treated in 1st-line with EGFR monoclonal antibody inhibitors (EGFRI) plus either FOLFOX or FOLFIRI from two randomized phase II trials (MACRO-2/PLANET) were included in the analysis. Pts were classified according to their primary tumor location as right-sided or left-sided. The main objective was to analyze the effect of primary tumor location on objective response rate (ORR), progression-free survival (PFS) and overall survival (OS). Differential responses in RAS WT pts according to tumor location were also evaluated.

Results: Pts with KRAS WT left-sided primary tumors (N = 209) versus right-sided primary tumors (N = 52) were analyzed. RAS was retrospectively determined in 69% of pts. Both KRAS and RAS WT left-sided had significantly superior ORR, median PFS and median OS compared with right-sided (Table).

Table: 583P

	KRAS WT		RAS WT	
	Right-sided (N = 52)	Left-sided (N = 209)	Right-sided (N = 33)	Left-sided (N = 148)
ORR (con˚rmed)				
Rate, %	25.0	46.9	33.3	52.7
OR (95% CI)	0.38 (0.19 – 0.75)		0.45 (0.20 – 0.99)	
P-value	0.004		0.044	
PFS				
Median, m	7.20	9.86	6.54	10.09
(95% CI)	(4.21 – 11.14)	(9.13 – 11.73)	(3.91 – 12.58)	(9.43 – 12.06)
HR (95% CI)	0.64 (0.44 – 0.92)		0.63 (0.40 – 0.99)	
P-value	0.016		0.044	
OS				
Median, m	13.57	27.73	13.57	32.79
(95% CI)	(8.44 – 26.02)	(24.97 – 36.17)	(8.41 – 34.23)	(26.45 – 39.85)
HR (95% CI)	0.47 (0.33 – 0.67)		0.44 (0.28 – 0.68)	
P-value	<0.0001		0.0002	

CI: confidence intervals; HR: hazard ratio; m: months; OR: odds ratio; ORR: objective response rate; OS: overall survival; PFS: progression-free survival WT: wild-type.

Conclusions: Pts with Left-sided primary tumors KRAS or RAS WT mCRC treated with first-line EGFRI plus chemotherapy have significantly improved efficacy outcomes as compared with pts with right-sided primary tumors KRAS or RAS WT mCRC

Clinical trial identification: MACRO-2 trial: NCT01161316, PLANET trial: NCT00885885

Legal entity responsible for the study: Spanish Cooperative Group for the Treatment of Digestive Tumors (TTD)

Funding: Amgen SA (PLANET), Merck. S. L. (MACRO-2)

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584P Predictive value of primary tumor location: Results from randomized phase II study of panitumumab + irinotecan versus cetuximab + irinotecan in patients with KRAS exon2 wild-type metastatic colorectal cancer (WJOG6510G)

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Background: WJOG6510G study compared cetuximab (Cmab) versus panitumumab (Pmab) in combination with irinotecan (IRI) for patients (pts) with KRAS exon2 wild-type (WT) metastatic colorectal cancer (mCRC) previously treated with fluoropyrimidine-, oxaliplation- and IRI- based chemotherapies. The study demonstrated that Pmab + IRI was not only non-inferior but slightly superior to Cmab + IRI in terms of PFS and OS (median PFS 4.3 months versus 5.4 months, HR 0.68, 95%CI 0.47-0.99, p = 0.040; median OS 11.5 months versus 14.9 months, HR 0.68, 95% CI 0.46-1.02, p = 0.06) (Sugimoto N, et al. ASCO-GI 2017). Here, we report predefined subgroup analyses of the study according to patient characteristics.

Methods: Pre-planned subgroup analyses investigated the homogeneity of treatment effects for PFS and OS across the following subgroups defined by age, gender, ECOG PS, histological type, prior resection of primary site, prior bevacizumab use, reason for oxaliplatin discontinuation, and primary tumor location. Cecum to transverse colon classified as right-sided CRC (RCRC), splenic flexure to rectum classified as left-sided CRC (LCRC).

Results: Totally, 120 (Cmab arm 59, Pmab arm 61) pts were eligible for the analyses. The subgroup analyses in PFS and OS revealed favorable tendency of Pmab arm for almost all factors. Among patients with LCRC (n = 104), Pmab+IRI significantly improved PFS and OS relative to Cmab+IRI (median PFS 4.2 months versus 5.6 months, HR 0.65, 95% CI 0.44-0.97, p = 0.030; median OS 11.1 months versus 15.4 months, HR 0.62, 95% CI 0.40-0.96, p = 0.030). In contrast, in RCRC tumors, comparable survival outcomes were observed between Cmab arm and Pmab arm.

Conclusions: Pmab + IRI for pretreated mCRC patients was associated with favorable PFS and OS compared to Cmab + IRI, especially with left-sided colorectal tumors.

Clinical trial identification: UMIN000006643

Legal entity responsible for the study: West Japan Oncology Group (WJOG)

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585P Differences in survival (sv) and clinicopathologic characteristics (cpc) between right and left-sided colorectal cancer (CRC): A CARESS-CCR group study

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Background: Until now, we have managed all CRC patients (pts) in the same way, However, emergent data show that location of primary tumor can have a prognostic and predictive value in metastatic setting. In this study, we analized differences in sv and cpc between right (R) and left-sided (L) CRC.

Methods: This prospective, multicentre observational study was conducted in coordination with 22 public-sector hospitals of Spain. Pts diagnosed with new CRC, stage I-IV and surgically treated, were included. We defined R-CRC as tumors originated in cecum, ascending colon, hepatic flexure or transverse colon, and L in splenic flexure, descending and sigmoid colon or rectum.

Results: Of 2694 recruited pts, 807 (30%) had R and 1887 (70%) L-CRCs. Most of cases were non-metastatic (89.9%), and males (63.5%). Mortality risk was higher for R-CRC and independent of stage (localised vs metastatic), with HR 1.69; 95% IC 1.24-2.29. Pts with R-tumors were slightly older than L, with a higher Body Mass Index (BMI), a greater predominance of women, non-smokers and regular Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) users. At presentation, they stayed asymptomatic, had elevated CA 19.9 or interval CRCs (diagnosed after negative screening test), and needed urgent surgery more frequently. They also showed special histologies, high grade and vascular invasion more often than L. Although differences in N and M staging were not detected, we observed more T1-T2 in L and more T3- T4 in R-tumors.

Table: 585P Differences in sv and cpc

	R-CRC	L-CRC	p
Sv 2 years (%, 95% IC)	87.9 (85.5 - 90.3)	91.9 (90.6 - 93.2)	0.002
Age (mean, SD)	69.8 ±10.5	67.8 ±11.0	<0.001
Woman (%)	43.0	33.7	<0.001
BMI (mean, SD)	28.1 ±5.0	27.5 ±4.7	0.008
Non-Smoker	55.4	45.2	<0.001
Regular NSAIDs user (%)	6.7	4.4	0.017
Asymptomatic (%)	10.5	7.5	0.017
Interval tumor (%)	12.3	7.1	0.038
Elevated Ca 19.9 (%)	18.8	13.5	0.029
Urgent surgery (%)	6.4	3.1	<0.001
Mucinous, signet-ring and medullary (%)	16.5	7.8	<0.001
High grade (%)	20.1	10.5	<0.001
Vascular invasion (%)	18.7	11.7	<0.001
T stage			<0.001
T1-T2	19.5	29.2	
T3-T4	80.1	67.8	

Conclusions: R and L-CRCs are different, and prognosis is better for L-tumors, independently of stage.

Legal entity responsible for the study: CARESS-CCR Study Group
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Disclosure: All authors have declared no conflicts of interest.

586P The prognostic value of sidedness of the primary tumor after local treatment for oligometastatic colorectal cancer: A Danish population based study

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Background: Metastasis directed therapy of metastatic colorectal cancer (mCRC) includes resection, radiofrequency ablation (RFA) and stereotactic radiotherapy (SBRT) of liver and/or lung metastases. The location of the primary tumor may influence survival in advanced disease. The aim of this study was to analyse the prognostic value of the primary tumors sidedness after local treatment of oligometastatic CRC in a national population based study.

Methods: Data was retrieved from the Danish Cancer Registry and the Danish National Patient Registry (DNPR) from all patients who underwent surgery for CRC between 2000-2013. Additional data from the DNPR included liver and/or lung metastasectomy, RFA or SBRT. Based on the surgical codes for primary tumor resection in DNPR, patients were grouped as right or left sided (including rectal cancer). Survival was calculated from the date of last recorded local treatment until death from any cause or end of follow-up. A Cox proportional hazard model was used to compute hazard ratios (HRs) for mortality between groups adjusting for age, gender, co-morbidity, nodal stage and site of local treatment.

Results: A total of 38131 patients had surgery for a primary CRC and 2912 patients underwent a total of 3602 metastasis directed procedures. The median age was 64.9 years (range 20-92 years) and 59% were male. Local treatment modalities comprised liver surgery (n = 1616), lung surgery (n = 1075), liver RFA (n = 705), liver SBRT (n = 124) and lung SBRT (n = 82). In the locally treated cohort 590 and 2264 patients were resected for a right and left sided primary tumor, respectively, (unknown primary location n = 58). For all patients (n = 2912), the median survival was 3.8 years (95% CI 3.6-4.0). For patients with a right and left sided tumor, the median survival reached 3.2 years (95% CI 2.7-3.5) and 4.0 years (95% CI 3.8-4.2), respectively. With left sided as the reference the adjusted HR 1.20(95%CI 1.07-1.38, p = 0.003).

Conclusions: In this national population based study, we report a longer median survival for CRC patients with a left sided primary as compared to right sided primary tumor after local treatment for liver and lung metastasis.

Legal entity responsible for the study: Department of Epidemiology, Aarhus University Hospital
Funding: Aarhus University
Disclosure: A. Boysen: Advisory board: Bayer. All other authors have declared no conflicts of interest.

587P Survival by sidedness of metastatic colorectal cancer (mCRC) treated with epidermal growth factor receptor antibodies (EGFR-Ab) in the refractory setting: A population-based study of 1509 patients

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Background: Sidedness of primary is an established prognostic factor in mCRC and recently has been shown to be an important predictive factor for patients (pts) treated with EGFR-Ab (always in combination with chemotherapy) in 1st and 2nd line settings. Limited data is available in 3rd line and beyond, where EGFR-Ab are used either as monotherapy or with chemotherapy. In Ontario, Canada, public funding of EGFR-Ab is restricted to chemorefractory disease. This study examines the impact of sidedness on overall survival (OS) in chemorefractory mCRC treated with EGFR-Ab monotherapy and combination.

Methods: This population-based retrospective cohort study used linked data from the Institute for Clinical Evaluative Sciences to evaluate mCRC pts treated in Ontario with EGFR-Ab from Jan 2006-Dec 2014. Over 99% of cases are captured via the Ontario Cancer Registry. The primary outcome was OS. Monotherapy v combination was compared by panitumumab (pani; funded only as monotherapy) v cetuximab (cet; funded only with chemotherapy) outcomes. Sidedness was determined by ICD-10 code as right (R; including transverse colon) or left (L).

Results: Of 67117 CRC pts,1553 received EGFR-Ab for refractory mCRC (429 R, 1080 L, 44 unknown). 71% received pani. R were more commonly female, with significantly shorter time (months, m) from diagnosis to EGFR-Ab therapy (mean ± SD: 28.7 ± 18.3 v 32.8 ± 19.2; p < 0.001). Median OS for R with any EGFR-Ab therapy was significantly worse than L: 30.5 v 39.3 m (HR 1.22; 95% CI 1.07-1.38; p = 0.0026); this was true for monotherapy (HR 1.22; 95% CI 1.05-1.42, p = 0.0089) with a near-significant trend for combination (HR 1.30; 95% CI 0.99-1.7, p = 0.055). For L, OS was identical between monotherapy and combination; for R there was a near-significant trend to longer survival with combination (HR 0.76; 95% CI 0.58-1.01, p = 0.058).

Conclusions: This large population cohort demonstrates that R sidedness is significantly predictive for survival with EGFR-Ab in refractory mCRC, consistent with findings in earlier lines of therapy. The differences are particularly seen with monotherapy. L sided cancers appear to benefit equally from monotherapy as combination.

Legal entity responsible for the study: Monash University
Funding: None
Disclosure: All authors have declared no conflicts of interest.

588P Differences in prescribing attitudes and treatment patterns between right-sided and left-sided mCRC in EU5 and the US

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Background: There is evidence to suggest that location of primary colorectal tumours has an impact on prognosis and efficacy of biological agents. Studies focus on *RAS WT* (*KRAS WT* and *NRAS WT*) mCRC, and have identified that left sided colon cancer (LSCC) is more common than right sided colon cancer (RSCC), is observed more in males and is associated with a better prognosis. RSCC on the other hand, is observed more in females and is associated with a worse prognosis. Patients with LSCC show a better response to EGFR inhibitors, whereas those with RSCC show a better response to VEGF inhibitors. This study aims to demonstrate the differences in prescribing habits by tumour location in EU5 and US and to evaluate the impact of new clinical data on real-world treatment patterns.

Methods: Between July 2016 and January 2017, a panel of oncologists in EU5 (n = 624) and US (n = 101) were asked to report on mCRC RAS WT patients and their treatments through the submission of online de-identified record forms.

Results: Out of 996 mCRC patients in EU5 and 821 in US, there are significantly more males with LSCC (57% & 56%) than RSCC (43% & 44%, p < 0.01), whereas for females the split between sides is not significantly different. Out of 2,106 1L *RAS WT* patients in EU5 and 198 in US, those with LSCC receive EGFR inhibitors more than RSCC (p < 0.01 & p < 0.05), but receive VEGF inhibitors less than RSCC patients (p < 0.01 EU5 only). There is no difference in treatment between LSCC and RSCC for 2L+ *RAS WT* patients in US, but in EU5 LSCC patients are prescribed VEGF inhibitors more than RSCC patients (p < 0.05). 'New clinical data' is a more frequent reason for using VEGF inhibitors or chemo-only on RSCC (14% & 4%) than for LSCC (7% & 2%, p < 0.01) in EU5. In US, the same is true for chemo-only patients with RSCC (18%) compared to LSCC (8%), whereas 'new clinical data' is a more significant reason for using EGFR inhibitors on LSCC (14%) than for RSCC (0%, p < 0.01).

Conclusions: 1L mCRC patients with LSCC receive EGFR inhibitors more than RSCC patients, whereas RSCC patients receive VEGF inhibitors more than LSCC patients, a trend not observed in 2L+. This supports the literature when considering that 'new clinical data' has been a significant reason for these prescribing patterns.

Legal entity responsible for the study: Ipsos Healthcare
Funding: None
Disclosure: All authors have declared no conflicts of interest.

589P Tumor sidedness and enriched gene groups for efficacy of 1st-line cetuximab (cet) treatment in metastatic colorectal cancer (mCRC)

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Background: Primary tumor location (PTL) has been shown to be not only a prognostic but also predictive factor for 1st-line cet treatment in mCRC. Molecular differences

between PTLs may contribute the sidedness-specific response to cet. We investigated genes associated with efficacy of cet treatment depending on tumor sidedness.

Methods: We enrolled 77 patients (pts) (57% males, median 63-y old, and 15% right-colon cancer) with KRAS exon 2 wild-type tumors from the JACCRO CC-05 or CC-06 trial of 1st-line therapy with cet plus FOLFOX or SOX, respectively. All pts' tissues were measured for expression levels of 2500 genes by HTG EdgeSeq Oncology Biomarker Panel using next generation sequencing for quantitative analysis of targeted RNAs. Univariate Cox regression analysis using log2 values of counts per million (CPM) was conducted for all genes that passed QC filtering in each sidedness (left [L]/right [R]) to assess the association with clinical outcomes. Further univariate Cox regression analysis was performed to define an optimal cutoff point for significant genes. Also, we performed a gene set enrichment analysis (GSEA) to identify classes of genes associated with outcomes in each side. Tumors proximal or from L flexure to rectum were defined as R-sided or L-sided, respectively.

Results: Sixty-nine of 77 pts were assessable for gene expression data. NOTCH1 high-expression (log2(CPM) $\geq$ 7.5) predicted significant longer progression-free survival (PFS) (median 14.7 vs. 11.1 m, HR 0.43, 95%CI 0.22-0.81, P = 0.01) and overall survival (OS) (median 42.8 vs. 26.5 m, HR 0.35, 95%CI 0.15-0.79, P = 0.01) in pts with L-sided tumor (n = 60) but not in R-sided tumor (n = 9).The GSEA showed that gene set of inflammatory response correlated with better PFS in both sides. The regulation of DNA replication gene set was associated with favorable OS but no gene set correlated with bad OS in L-side. Several types of gene set were identified to predict better or worse outcomes in R-side.

Conclusions: Our data suggest that gene expression signatures may explain differences in cet efficacy dependent on tumor sidedness. NOTCH1 may potentially discriminate favorable responders to cet in pts with L-sided tumors.

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Legal entity responsible for the study: Japan Clinical Cancer Research Organization: JACCRO

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590P Correlation between RECIST-criteria, morphologic response by CT and pathologic regression in hepatic metastasis secondary to colorectal cancer: The AVAMET study

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Background: The RECIST criteria may be limited in assessing response to biologic agents such as bevacizumab (BVZ). Computed tomography-based morphologic criteria (CTMC) might be an alternative to evaluate response in these cases. The aim of this trial was to evaluate the correlation of overall objective responses evaluated by RECIST with CTMC and the pathologic response (pR) after the resection of liver metastases from colorectal cancer.

Methods: Patients with $\leq$ 4 resectable CLM, with no prior chemotherapy for metastatic disease, received 3 cycles of capecitabine/oxaliplatin (XELOX)+BVZ. Response was evaluated using RECIST criteria and CTMC. For CTMC, metastasis was assigned to 1 of 3 groups (Table): CTMC were defined as optimal (metastasis changed from a group 3 or 2 to a 1), incomplete (group changed from 3 to 2), and none (the group had not changed or increased). Those patients without progression, received another cycle of XELOX prior to surgery. After surgery, BVZ + XELOX was given for up to 4 additional cycles. pR was scored as minor ($\geq$50% of residual tumor cells), major (1-49% residual tumor cells), and complete (no residual tumor cells detected).

Results: 83 patients were recruited. 68 were evaluated by RECIST and 67 of them by CTMC; 60 underwent surgery, 51 with metastases resection and histologically analysis. 33 of 68 pts reached partial response by RECIST (49%, 95%CI 37-60%) and 58 had optimal (26) or incomplete (32) response by CTMC (85%, 95%CI 75-92%). Complete (12) or major (30) pR was achieved in 42 of 51 pts (82%, 95%CI 70-90%). Although there was no correlation between the RECIST criteria, CTMC and pR, CTMC was more specific for predicting complete/major pR than RECIST (36 of 42, CTMC vs. 24 of 42, RECIST, p=.0038). In patients with liver resection overall survival at 48 months was 65.8%.

Table: 590P

Computed Tomographic Morphologic Groups

	Computed Tomographic Tumor Characteristics		
Morphology Group	Overall Attenuation	Tumor-Liver Interface	Peripheral Rim of enhancement
3	Heterogeneous	Ill defined	May be present
2	Mixed	Variable	If initially present, partially resolved
1	Homogeneous and hypoattenuating	Sharp	If initially present, completely resolved

Conclusions: CTMC was more specific for predicting complete/major pR than RECIST criteria. After liver metastases resection, 82% of patients had complete or major pR. CTMC seem to be a better surrogate marker of objective pR than RECIST.

Clinical trial identification: 2011-000143-24

Legal entity responsible for the study: Grupo GEMCAD

Funding: Roche

Disclosure: All authors have declared no conflicts of interest.

591P Tumor staging with magnetic resonance imaging after neoadjuvant chemoradiation for locally advanced rectal cancer and comparison of pathologic staging

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Background: This study was designed to evaluate the role of magnetic resonance imaging (MRI) on preoperative restaging locally advanced rectal cancer after neoadjuvant chemoradiotherapy (CRT), in order to facilitate individualization of surgical management.

Methods: We analyzed 106 patients who had received neoadjuvant CRT underwent a MRI before and after CRT. All patients underwent restaging MRI followed by surgery after the end of CRT. The primary endpoint of the present study was to estimate the accuracy of post-CRT MRI as compared with pathologic staging.

Results: Pathologic T classification matched the post-CRT MRI findings in 38(35.8%) of 106 patients. Sensitivity in T0, T3 and T4 was 25%, 50% and 80% respectively. Specificity in T0, T3 and T4 were 80,2%, 69,7% and 99% respectively. Sensitivity in N0 and N1 were 78,5% and 38,4% respectively. Specificity was 18,2% in N0 and 91,4% in N1. 43 (40,5%) of 106 patients were overstaged in T classification. Pathologic N classification matched the post-CRI MRI findings in 71 (66,7%) of 106 patients. 21(19.8%) of 106 patients were overstaged in N classification. 25 patients (23,6%) achieved T downstaging and 14 patients N dowstaging (13,2%) on restaging MRI after CRT. 24(22,6%) of 106 patients who had been downstaged on MRI after CRT were confirmed on the pathological staging with same stage (T and N).

Conclusions: MRI has low accuracy for restaging locally advanced rectal cancer after preoperative chemoradiation so it is currently not consistent enough for clinical application.

Legal entity responsible for the study: Hospital Ramón y Cajal

Funding: None

Disclosure: All authors have declared no conflicts of interest.

592P Quality of life in patients with liver metastases from colorectal cancer treated with first-line selective internal radiotherapy (SIRT): Results from the FOXFIRE prospective randomized studies

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Background: Quality of life (QoL) in patients with colorectal cancer and liver metastases treated with selective internal radiotherapy (SIRT) using Yttrium-90 resin microspheres combined with FOLFOX (standard chemotherapy) has not been compared to FOLFOX alone. We report QoL results from a prospectively pooled analysis of 3 multicentre randomized trials: FOXFIRE, FOXFIRE-Global and SIRFLOX.

Methods: Patients were randomized to FOLFOX or FOLFOX+SIRT in 14 countries. Second-line therapy was permitted upon disease progression. EORTC QLQ-C30 and EuroQoL EQ-5D (3 level) questionnaires were given to all patients at baseline, 2-3, 6 and 12 months from starting treatment and yearly thereafter, and at disease progression. We compared QoL scores between arms at each timepoint, calculating mean differences adjusted for baseline scores, using a 5% significance level. No missing data imputation was performed.

Results: 1103 patients were randomised overall. Questionnaire response rates ranged from 92% (1010/1103) at baseline to 33% (163/493) at 24 months. Patients randomised to SIRT showed significantly ($p < 0.05$) worse scores on 3 of 6 QLQ-C30 functioning scales and 3 of 9 symptom scales (fatigue, nausea and vomiting, appetite loss) at 4-8 weeks after treatment (2-3 months from baseline). SIRT patients had significantly better functioning scores on 3 of 6 scales at disease progression, and significantly less dyspnoea or constipation. Almost no other QLQ-C30 scales showed significant differences at 6, 12 or 24 months. The EQ-5D showed a statistically significant decrement of 0.02 in patients in the SIRT group 2-3 months from baseline, but no differences at other timepoints.

Conclusions: This analysis has shown that QoL is slightly impaired in functioning and symptom domains 4-8 weeks after treatment with SIRT+FOLFOX compared with FOLFOX alone, but slightly better when measured at disease progression. These differences were consistent between the QLQ-C30 and EQ-5D instruments. The differences detected were not large enough to be considered clinically significant.

Clinical trial identification: FOXFIRE ISRCTN83867919; SIRFLOX NCT00724503; FOXFIRE-Global NCT01721954

Legal entity responsible for the study: University of Oxford

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Disclosure: I. Chau: Advisory Board: Sanofi Oncology, Eli Lilly, Bristol-Myers Squibb, MSD, Bayer, Roche, Five Prime Therapeutics. Research funding: Janssen-Cilag, Sanofi Oncology, Merck Serono, Novartis. Honorarium: Taiho, Pfizer, Amgen, Eli Lilly, Gilead Science. S. Love: Grants from: Cancer Research UK, Sirtex Medical and non-financial support from Sirtex Medical. J. Moschandreas: Grants from Cancer Research UK, Sirtex Medical and non-financial support from Sirtex Medical. P. Virdee: Grants from Cancer Research UK, Sirtex Medical and non-financial support from Sirtex Medical. P. Tait: Medical advisor and medical proctor for Sirtex medical. H. Wasan: Grants, personal fees, non-financial support and other uncompensated work from Sirtex Medical. G. Van Hazel: Compensation for participation in advisory committees from Sirtex. P. Gibbs: Personal fees from Sirtex. R. Sharma: Research funding, honoraria and consultancy fees from Sirtex Medical. All other authors have declared no conflicts of interest.

593P Quality of life (QoL) analyses in patients with RAS wild-type (wt) metastatic colorectal cancer (mCRC) treated with first-line FOLFOX-4 ± cetuximab in the phase 3 TAILOR trial

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Background: In the phase 3 TAILOR trial, adding cetuximab to first-line FOLFOX-4 significantly improved progression-free survival (PFS), overall survival (OS), and overall response rate (ORR) in patients with *RAS* wt mCRC. Here we present QoL analyses.

Methods: TAILOR is a randomized phase 3 trial that includes a modified intention-to-treat population of 393 patients from China with *RAS* wt mCRC treated with FOLFOX-4 ± cetuximab. The primary endpoint of TAILOR is PFS based on independent review; secondary endpoints include OS, ORR, and QoL. QoL is investigated using the European Organisation for Research and Treatment of Cancer QoL questionnaire core-30 (EORTC QLQ-C30). QoL assessments were planned to be performed at baseline, every 8 weeks of treatment thereafter, and at the final tumor assessment. Patients with *RAS* wt tumors are considered evaluable for QoL if they provide ≥ 1 evaluable EORTC QLQ-C30 from screening to end of evaluation. Pattern-mixture modeling is used to compare QoL between treatment groups by taking into account dropout pattern and other covariates.

Results: Among 393 patients with *RAS* wt tumors, 390 were evaluable for QoL. Before adjustment for several factors (treatment, time, dropout pattern, age, sex, ECOG performance status, number of disease sites, liver-only metastases, and interaction between treatment and dropout pattern), global health status/QoL showed slightly more deterioration in the FOLFOX-4 + cetuximab arm vs FOLFOX-4 arm; however, when these factors were included in the analysis model, the difference between treatment groups was not considered clinically relevant. Similar findings were obtained upon analogous evaluation of social functioning, an individual QoL-related dimension of interest in mCRC.

Conclusions: Adding cetuximab to first-line FOLFOX-4 significantly improved PFS, OS, and ORR without negatively impacting QoL in TAILOR study patients with *RAS* wt mCRC, consistent with observations from earlier cetuximab pivotal trials. These observations confirm cetuximab in combination with FOLFOX-4 as a standard-of-care first-line treatment regimen for patients with *RAS* wt mCRC.

Clinical trial identification: NCT01228734

Legal entity responsible for the study: Merck KGaA, Darmstadt, Germany

Funding: Merck KGaA, Darmstadt, Germany

Disclosure: J. Li: Research funding: Merck Inc., Roche-Peru. W. Chen, J. Chen: Employment: Merck Serono. C.P. Pescott: Employment: Merck KGaA, Darmstadt, Germany. All other authors have declared no conflicts of interest.

594P Implementation, participation and satisfaction rates of a web-based decision support tool for patients with metastatic colorectal cancer

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Background: The use of decision support tools facilitates shared decision-making, but effective implementation of these tools with adequate patient and provider participation is challenging. Our study aims to effectively implement a newly developed patient-centred decision support tool for patients with metastatic colorectal cancer with sufficient patients' and providers' participation and satisfaction.

Methods: We conducted a patients' and oncologists' needs assessment and developed a decision support tool consisting of a consultation tool and web-based information about treatment options. Between July 2016 (launch) and February 2017, we measured patient participation with log in rates and time spent by online tracking and calculated participation sum scores (low, intermediate and high). Patient satisfaction was voluntarily obtained during online support. We measured oncologist participation in 11 centers by the number of oncologists that handed out at least 1 consultation tool. Satisfaction was measured by structured interviews and a survey.

Results: Implementation rates differed between 3 and 72 handed out (median 23) consultation tools per centre with a median patients' log in rate of 57% (range 39-83%). The majority of patients (68%) had an intermediate high or high participation sum score. The median time spent during online support was highest for questions about patients' perspective (5 mins) and colorectal cancer information (4 mins). Patient satisfaction was 76%. Oncologists' participation per centre ranged from 25 to 100%. The average rating of the decision support tool was 7.8 (scale 1 to 10) by participating

oncologists and 7.3 by other healthcare providers. Several thresholds for implementation were a negative attitude towards shared decision-making and oncologists' fixed treatment preferences.

Conclusions: Implementation of our decision support tool succeeded and patient and oncologist satisfaction was above average. Patients' log in rates differed considerably between participating hospitals while patient online participation was generally high. The most important faced challenge remains to overcome providers' negative attitude towards shared decision-making.

Legal entity responsible for the study: Academic Medical Center - University of Amsterdam

Funding: Dutch Digestive Foundation

Disclosure: All authors have declared no conflicts of interest.

595P Quality-of-life in patients with metastatic colorectal cancer (mCRC) treated with aflibercept and FOLFIRI – Interim results of the non-interventional AIO study QoLiTrap

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Background: The anti-angiogenic fusion protein Aflibercept targets VEGF-A, VEGF-B and PlGF. Aflibercept in combination with FOLFIRI is approved in patients with mCRC that is resistant or has progressed after oxaliplatin-containing therapy.

Methods: QoLiTrap (AIO-LQ-0113) is an international (Austria, Germany, Switzerland) non-interventional study with a recruitment target of 1500 patients. Primary goal is to evaluate Quality-of-life (QoL) in mCRC patients treated with aflibercept + FOLFIRI using the EORTC-QLQ C30 questionnaire at baseline and before every cycle.

Results: For this interim analysis (data cut-off: 02 March 2017) 576 patients (mean age: 64.7 ± 10 years; 65.1% male, 50.5% with documented RAS mutation, ECOG 0-1: 85.6% of patients) who completed the baseline and at least 2 post-baseline EORTC-QLQ C30 questionnaires were evaluated. Aflibercept was administered for a median number of 6 (and up to 55) cycles. Patients had a median global health score of 58.3 which decreased moderately (mean change -4.0, $p < 0.0001$) within the first 12 weeks of therapy with no significant worsening in gastrointestinal, dyspnea, and sleep disturbance symptom scales. 202 patients receiving study therapy as 2nd line treatment were pretreated with anti-EGFR antibody and/or bevacizumab. Within this subgroup, CR and PR was documented for 26% and SD for 47% of evaluable patients as best response to aflibercept and the median PFS amounted to 8.2 months [95% CI 6.0 – 9.0]. No difference between PFS of RAS wildtype and RAS mutated patients was observed. No new safety signals were identified from the current interim analysis.

Conclusions: The current interim analysis indicates that aflibercept + FOLFIRI in mCRC patients under routine conditions was accompanied by a moderate decline in global health status. Preliminary efficacy results are encouraging, also for patients pretreated with anti-EGFR antibody and/or bevacizumab, who showed a disease control rate of 73% in second line aflibercept therapy. This study is supported by Sanofi-Aventis Deutschland GmbH.

Clinical trial identification: AIO-LQ-0113

Legal entity responsible for the study: Sanofi Aventis GmbH

Funding: Sanofi Aventis Deutschland GmbH

Disclosure: R. von Moos: Advisory board: Sanofi, Roche, Merck. Research grant: Amgen, Merck. G. Derigs: Advisory activities: Janssen, Roche, Clegene. F. Scholten: Advisory activities: BMS, Celgene. Honorarium: Janssen, Sanofi. Poster creation: Sanofi. R.D. Hofheinz: Advisory Board: Sanofi. Honorarium: Sanofi. All other authors have declared no conflicts of interest.

596P Chemotherapy-induced thrombocytopenia (CIT) in metastatic colorectal cancer (mCRC) patients

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Background: Thrombocytopenia is a common hematologic toxicity of myelosuppressive chemotherapy and can complicate a patient's care.

Methods: This is a descriptive secondary analysis of data from two large clinical trials of mCRC patients – 1,078 treatment-naïve patients receiving fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) and 1,067 previously-treated patients receiving fluorouracil, leucovorin, and irinotecan (FOLFIRI) – to investigate the frequency and clinical consequences of CIT. Evidence of CIT was studied in two ways: 1) recorded platelet counts throughout the study (overall and by grade: $<100\text{-}75 \times 10^9$/L [grade 1]; <75-50 [grade 2]; <50-25 [grade 3]; <25 [grade 4]); and 2) the occurrence of "thrombocytopenia" as an adverse event that directly resulted in platelet transfusion, chemotherapy discontinuation, and/or chemotherapy dose change/delay. The number, duration, and timing (with respect to chemotherapy cycle) of CIT episodes and the co-occurrence of neutropenia and/or anemia (overall and by grade), were also analyzed but not reported in this abstract.

Results: Evidence of CIT based solely on platelet count was relatively common in the FOLFOX4 study (37% of patients had ≥1 platelet count $<100 \times 10^9$/L) and less frequent in the FOLFIRI study (4%), during a median follow-up of approximately one year in each study. Evidence of grades 2, 3 and 4 thrombocytopenia were observed in 15%, 2%, and 1% of FOLFOX4 patients, respectively, and in 1%, <1%, and 0%, of FOLFIRI patients, respectively. Thrombocytopenia as an adverse event resulting in one of the clinical outcomes of interest occurred a total of 433 times across the two studies (FOLFOX4: 406; FOLFIRI: 27). Most events (97%) were addressed solely through a chemotherapy dose change and/or delay, but there were 4 events that were managed exclusively by chemotherapy discontinuation and 10 instances when a platelet transfusion was required (2 of which also led to chemotherapy discontinuation).

Conclusions: In mCRC patients receiving chemotherapy, thrombocytopenia can pose a real clinical problem, commonly leading to chemotherapy delays and/or dose reductions and in some cases, necessitating platelet transfusion and cessation of chemotherapy treatment.

Clinical trial identification: This was a secondary analysis of data from two clinical trials: NCT00364013 and NCT00339183

Legal entity responsible for the study: Amgen Inc

Funding: Amgen Inc

Disclosure: K. Cetin: Employee of Amgen Inc and ownership of Amgen Inc stock. A. Toler: Employed by Amgen Inc M. Eisen: Employee of Amgen Inc and ownership of Amgen Inc stock. G.A. Soff: Research support from Amgen Inc. Consulting fees from Amgen Inc. Research funding from Janssen Pharmaceuticals.

597P Real world use of palliative systemic therapy (tx) in patients (pts) with metastatic early onset colorectal cancer (mEOCRC) within a UK specialist cancer centre

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Background: The incidence of EOCRC, defined as CRC diagnosed in pts< 50 years old, is increasing. Current literature relating to the palliative systemic tx used, its efficacy, tolerability and outcomes in this group is sparse.

Methods: Retrospective analysis of pts with mEOCRC treated with systemic tx at the Royal Marsden Hospital (RMH) between Jan 2009 – Dec 2014 was conducted.

Results: 114 pts had palliative systemic tx. 93 had mEOCRC at diagnosis of whom 51% were male, median age 43 (range 21-49), 90% performance status ≤1. 72% had left (L) sided tumours. 4% had signet cells. 2 pts had known hereditary syndromes. 72% had

Table: 597P

Metastatic tx line	1	2	3	4
N	114	78	40	15
Median PFS, months	6.9	5.0	2.0	3.9
Best Response (%)	CR 4 PR 40 SD 23 PD 32 NA 1	CR 1 PR 17 SD 26 PD 51 NA 5	PR 8 SD 23 PD 69	PR 7 SD 13 PD 73 NA 7
mOS from diagnosis if last line of tx, months	9.0	14.9	18.7	31.7

liver, 20% peritoneal and 20% lung metastases (met). All 114 pts had ≥1 line of doublet cytotoxic tx. The most commonly administered regimens were: 15% FOLFIRI+ bevacizumab (Bev), 15% FOLFIRI, 11% CAPOX, 10% FOLFOX+ Bev. 12% of tx was given within trials. 38% of pts had tx delays and 38% dose reductions or one agent of a combination tx discontinued early, during their the first line tx. 19% had radiofrequency ablation to liver or lung met. Median overall survival (mOS) in pts presenting with mEOCRC: 18.5 months (95% C.I 14.3-22.6). In addition to BRAF mutant pts, the groups below also trended towards a lower mOS, months (95%C.I): -Younger age: Age 20-29=8.3 (2.6-28.6), 30-39=16.1 (9.6-22.6), 40-49=21.2 (14.9-27.7) -Right (R) sided tumour: R = 13.7 (8.3-18.7) vs L = 20.2 (14.9-27.7) -Signet cells =7.0 (NA) vs No signet cells =18.7 (14.3-22.6) -Fewer lines of systemic tx (Table) The majority of *KRAS* Wild Type (WT) pts (n = 46) had cetuximab or panitumumab. mOS was 21.7 months (95% C.I 16.0-27.7) for WT vs 15.8 months (95% C.I 9.9-21.2) in mutant pts.

Conclusions: Pts treated with sequential combination systemic tx had a better mOS. However, pts with mEOCRC appear to have lower response rates, progression free survival (PFS) and OS when compared to recently published randomised trials. This suggests a more aggressive disease phenotype that warrants further research and tx development.

Legal entity responsible for the study: Royal Marsden Hospital, UK

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Disclosure: All authors have declared no conflicts of interest.

598P PD-L1 expression in resected colorectal adenocarcinomas is associated with micrometastais

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Background: Programmed cell death 1 (PD-1) and its ligand (PD-L1) are key suppressors of the cytotoxic immune response. PD-L1 expression on tumor cells may be induced by the immune microenvironment, resulting in immune escape, and an adverse prognosis in many malignancies. In colorectal carcinoma the response to PD-1/PD-L1 inhibition is correlated with microsatellite instability. However, little is known about the clinicopathologic, molecular, and prognostic characteristics of colorectal carcinoma with PD-L1 expression. In surgically resected colorectal adenocarcinoma, micrometastasis should be crucial for recurrence, and micrometastasis may be related to PD-L1. The aim of this study is to assess the PD-L1 expression and its association with clinicopathologic manifestations.

Methods: PD-L1 expression was evaluated in 176 resected colorectal adenocarcinomas using tissue microarrays. Immunohistochemical staining was performed to evaluate the expression of PD-L1. The relationship of clinicopathologic manifestations and PD-L1 expression in colorectal cancer were evaluated by chi-squared test, Kaplan-Meier survival and Cox regression test.

Results: High PD-L1 expression was present in 52.8% colorectal adenocarcinoma and was not related pathologic T or N stage. High PD-L1 expression was associated with decreased recurrence rate ($p < 0.001$), better disease-free survival ($p < 0.001$). Cox regression analysis revealed that pathologic N stage and High PD-L1 expression was an independent prognostic factors of disease-free survival ($p < 0.001$).

Conclusions: High PD-L1 expression is an independent prognostic factor, such as pathologic stage in colorectal adenocarcinoma. PD-L1 expression is independent prognostic factor, relating immune response to micrometastasis and immune suppression by PD-L1 may not be effective in micrometastasis of colorectal adenocarcinoma.

Legal entity responsible for the study: None

Funding: None

Disclosure: All authors have declared no conflicts of interest.

599P Real life registry data of primary localisation of a well-defined colon cancer population of western Austria (Salzburg, Tyrol and Vorarlberg), eastern Switzerland (St. Gallen and Graubünden) and Liechtenstein

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Background: Primary tumors arising from different regions of the colon are biologically distinct; thus location is associated with different features such as microbiota and molecular alterations. Recently, retrospective analysis of phase III trials have shown better prognosis and a significant benefit of anti-EGFR antibodies in left sided RAS wild-type metastatic colon cancer patients. Epidemiological analysis of colon cancer patients from the neighbouring Cancer Registries of Salzburg, Tyrol and Vorarlberg, St. Gallen, Graubünden, and Liechtenstein was to support different prognostic value of left-and right-sided colon cancer.

Methods: 7626 patients with pathologically confirmed colon cancer diagnosed between 2005 and 2015 were identified from the database of the population-based cancer registries of Western Austria, Eastern Switzerland and Liechtenstein. Patients were categorized in two groups: Right-sided colon cancer (RCC) including tumors of the colon transversum and left-sided colon cancer (LCC). Analysis was conducted separately for UICC stages III and IV. Survival curves were estimated applying the Kaplan-Meier method; for comparison of RCC and LCC cohorts the Logrank test was applied. Tumor stage and localisation are shown in the following table.

Table: 599P

Staging UICC	RCC	LCC	Total
I	626 (16.7%)	918 (23.6%)	1544 (20.2%)
II	1091 (29.2%)	979 (25.2%)	2070 (27.1%)
III	995 (26.6%)	1016 (26.1%)	2011 (26.4%)
IV	863 (23.1%)	807 (20.8%)	1670 (21.9%)
X/nos	164 (4.4%)	167 (4.3%)	331 (4.3%)
Total	**3739 (100.0%)**	**3887 (100.0%)**	**7626 (100.0%)**

Results: Tumor location per se in stage III and IV colon cancer in the current retrospectively, epidemiological study, revealed a significantly better overall survival for LCC than for RCC in stage III and IV in a univariate analysis. After stratification by age, hazard ratio was 0.91 (95% Confidence interval 0.78-1.07) in stage III and 0.75 (95% confidence interval 0.66-0.84) in stage IV, thereby confirming recent, retrospective data from large phase III clinical trials (FIRE-3, CHRYSTAL; PEAK and PRIME).

Conclusions: Real life registry data of a well- defined colon cancer population confirm retrospective clinical trial data that LCC in stage III and IV carry a more favourable outcome than RCC, even in the era of modern chemo-immunotherapy.

Legal entity responsible for the study: Alois H. Lang

Funding: Krebsregister Vorarlberg

Disclosure: All authors have declared no conflicts of interest.

600P Improving visualization and adherence by converting the Dutch colorectal cancer guidelines into decision trees: The Oncoguide project

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Background: Clinical guidelines are designed to prevent undesired practice variation where high quality evidence or expert consensus is available. However, reading and interpretation of text-based guidelines is time-consuming and might be difficult to apply in routine daily practice. Therefore, the aim of our study is to examine the feasibility of converting the Dutch multidisciplinary colorectal cancer guideline recommendations into data driven algorithms (decision trees) to facilitate guideline usage.

Methods: We converted the most recent Dutch colorectal cancer guideline (published in 2014) into decision trees modelled by decision nodes representing patient or disease characteristics ultimately branching into guideline recommendations. Where not evidence-based, decision trees were discussed with an expert panel until agreement was reached. Thereafter, the developed decision trees were published in open access decision support software.

Results: In total, we developed 34 decision trees driven by 101 decision nodes. Decision trees focused on recommendations for diagnostics (n = 1) staging (n = 10), treatment (colon: n = 1, rectum: n = 5, both: n = 9), pathology (n = 4), follow-up (n = 3) and 1 overview decision tree. We identified guideline recommendation information gaps, for example specific surgical policy related to (the number of) lung metastases, a recommendation about follow-up schemes after resection or local treatment (e.g. RFA) of metastases and the period between neo-adjuvant treatment and re-staging. It was

difficult to convert some of the guideline recommendations into decision trees (i.e. 'consider PET-CT scan to exclude extrahepatic metastases'), related to non-conclusive evidence on specific topics.

Conclusions: Converting the Dutch colorectal cancer guideline into decision trees is feasible, but presents several challenges. Using decision trees may (I) improve guideline adherence or more conscious guideline deviation; (II) improve guideline (adherence) evaluation from cancer registries; and (III) ultimately learn from clinical cases with documented motivation for guideline deviation.

Legal entity responsible for the study: Comprehensive Cancer Center Netherlands

Funding: Academic Medical Center - University of Amsterdam

Disclosure: All authors have declared no conflicts of interest.

601P Colon and rectal cancer incidence are rising among young Europeans: Results from the cancer registry of Crete

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Background: Colorectal cancer (CRC) incidence is declining rapidly overall in most European countries. Curiously, in the United States, a worrisome increase in incidence has recently been reported among young adults. We report the first study on this specific age group in the European population.

Methods: This retrospective study was conducted in Crete, Greece using data on malignant neoplasms of the colon (ICD-10: C18), rectosigmoid junction and rectum (ICD-10: C19-20). Data were obtained from the database of the regional Cancer Registry of Crete () and coded according to the international classification system for Oncology (ICD10-O-2). Information on patient's demographic profile, personal and family medical history and lifestyle factors (smoking habits, alcohol consumption) were also available. The analysis was performed in STATA, while all tests were at $a = 0.05$.

Results: The mean age-specific incidence rates (ASpIR) of CRC patients <50 years at diagnosis were 5.1/100,000/year, while for patients≥50 years the ASpIR was 150/100,000/year. The rates were significantly higher for male patients compared to females ($p = 0.02$), especially between the ages of 30 and 70 years. Contrary to that, females aged 20-24 years presented slightly higher ASpIR comparing to males. Focusing on patients <50 years, significant percentage changes of incidence rates per year ($p < 0.05$) are observed for both colon and rectal cancer. The age group of 20-34 years presented 29.7% increase from 1992 to 2013, while the increase for the period 2014 to 2024 is expected to reach 36.9%. Similar increases were observed in the age group of 35-49 years (2003-2013: + 25.1%, 2014-2024: + 28.5%). Interestingly, and despite the fact that screening is voluntary in Greece, a decline in incidence rate by 31.4% was observed in adults ≥50 years old, more predominantly after 2008.

Conclusions: We confirmed in European population an increased incidence of CRC under the age of 50 and a worrisome prediction for the near future. Since mortality in young adults with CRC is high, efforts to promote research and awareness among patients and physicians about the unique characteristics of early-onset CRC are critical.

Legal entity responsible for the study: Cancer registry of Crete

Funding: None

Disclosure: All authors have declared no conflicts of interest.

602P Epidemiology of colorectal cancer in Korea: Korean National Health insurance bigdata analysis

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Background: This study was conducted to demonstrate the epidemiology of colorectal cancer (CRC) in Korea using the by analysis of big data using the Korean National Health Insurance Service (NHIS).

Methods: We analyzed the NHIS database of patients admitted hospitals which received its quality assessment of CRC between 2011 and 2014.

Results: We included 71,513 colorectal cancer patients. Median follow-up duration was 3.2 years (range 0.003-5.5 years). Male patients were 60.1% and median age was 65 years old (interqurtile range 56-73). The stage at diagnosis was stage I in 22.0%, stage II 29.0%, stage III 35.6%, stage IV 12.9%. As primary site according to surgery code, colon is 61.7% and rectum is 38.3%. Patients with adenocarcinoma were 96.5%. Survival probability at 5 year elderly patients (^{3} 70 years old) showed worse survival rate than that of patient with age <70 [HR 2.24, 95% confidence interval (CI) 2.17 -2.32]. By stage, survival probability at 5 year is 91.9% with stage I, 82.8% with stage II, 73.8% with stage III, and 30.4% with stage IV.

Conclusions: These results show epidemiology and survival of CRC in Korea. Our study was the first to describe these data for colorectal cancer at a nationwide level.

Legal entity responsible for the study: Sun Kyung Baek

Funding: None

Disclosure: All authors have declared no conflicts of interest.

603P Watch and wait versus surgery with pathological complete response: Single institution experience

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Background: Neoadjuvant chemoradiation therapy improves local control, may lead to significant tumor regression and even complete pathological response. We compared patients managed by watch and wait approach and those submitted to surgery with pathological complete response.

Methods: We included patients with rectal adenocarcinoma who had received neoadjuvant long-course chemoradiation therapy (45-50.4 Gy in 25-28 daily fractions with concurrent fluoropyrimidine-based chemotherapy) between July 2003 and December 2012. After, we compared outcomes between two groups: 1) 39 patients managed with watch and wait (WW) approach after clinical complete response; 2) 68 patients submitted to surgery and had pathological complete response (pCR). The primary endpoint was relapse-free survival (RFS).

Results: The median age was 63.5years of age (43-81y) for WW and 60 (29-86y) for pCR. After median follow up of 73 months, of 39 patients managed by watch and wait, 8 (20%) patients had local relapse, 4 (10%) patients had distant relapse, and 3 (7.5%) patients had both and of 68 patients with pCR, 4 (5.8%) patients had local relapse, 5 (7.3%) patients had distant relapse, and 3 (4.4%) patients had both. Salvage surgery was possible in 5 (62.5%) patients after local relapse and 1 (33%) patient after local and distant relapse in WW group, but was not possible in any patient in pCR group. Twenty-five (62.5%) patients have sustained complete clinical response without any surgery in WW group. Local relapse was 3 times higher in WW group (OR 3 – CI:1.09-8.69) and distant relapse were equal (OR: 1.3 – CI:0.43-4.26). The 3- and 5-year RFS was 84.8% and 75.1%, respectively, and was significant better in pCR than WW (HR: 2.46 CI: 1.13-5.49 – p: 0.02). The 3- and 5-year OS was 89.3% and 79.1%, respectively, and was similar in both groups (HR: 1.43 CI: 0.64-3.27 – p: 0.36). Permanent colostomy was 2.6 higher in pCR group (CI:1.02-6.69).

Conclusions: The watch and wait approach had worse RFS without impact on overall survival. Radical rectal surgery was avoided in 62.5% of patients selected and salvage surgery was possible in 62.5% of patients who had local relapse in WW group. The odds of permanent colostomy were 2.6 higher in pCR group.

Legal entity responsible for the study: INCA - Instituto Nacional de Cancer

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Disclosure: All authors have declared no conflicts of interest.

604P A retrospective cohort study evaluating the safety and efficacy of TAS-102 in patients with metastatic colorectal cancer [HGCSG1503]: Updated analysis

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Background: The J003 trial and RECOURSE trial revealed the safety and efficacy of TAS-102 for patients with metastatic colorectal cancer (mCRC). In March 2014, TAS-102 was approved in Japan, however, there are few studies exploring the efficacy and safety of TAS-102, particularly in the daily practice use. Therefore, we performed this retrospective analysis in order to investigate the real-world clinical practice of TAS-102 for patients with mCRC.

Methods: We retrospectively analyzed the clinical data of 411 patients who received TAS-102 in the multi-institutional retrospective study (HGCSG1503). This study was analyzed by CTCAE v4.0 for adverse events (AEs), RECIST v1.1 for response rate (RR)/ disease control rate (DCR), and Kaplan-Meier method for progression free survival (PFS) and overall survival (OS).

Results: Patients characteristics were as follows; male/female 218/193, median age 66 (range 33-88), ECOG PS (0/1/2/3) 170/190/43/8, KRAS Exon2 wild/mutant 210/187 (14 patients; KRAS Exon2 was not tested). The initial starting dose was 70 mg/m^2 (n = 326, 79.3%) and reduced dose (n = 85, 20.7%). Dose reductions were required in 101 patients (24.6%). The common ≥grade 3 AEs were neutrophil count decreased (48.1%), white blood cell decreased (34.8%), and anemia (28.7%). RR and DCR were 0.5% and 37.2%, respectively. Median PFS and OS were 2.2 and 7.3 months. In analysis on the relationship between ECOG PS 0-1 and PS 2-3, DCR was 38.7% vs. 26.7% (p = 0.140), median PFS was 2.3 vs. 1.5 months (HR 2.000, p < 0.001), and MST was 8.1 vs. 3.4 months (HR 2.778, p < 0.001).

Conclusions: In this analysis, TAS-102 in the real-world clinical practice showed slightly higher anemia to the previous pivotal clinical trials. Although the efficacy in patients with PS 0–1 was similar to the previous reports, TAS-102 did not show the efficacy for patients with PS 2-3.

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Legal entity responsible for the study: Non-profit organization: Hokkaido Gastrointestinal Cancer Study Group

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605P Preliminary results on germline and somatic molecular investigations in Romanian Lynch syndrome patients

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Background: Up to 30% of colorectal cancers (CRCs) have evidence of a familial component, and about 5% are thought to be due to inherited mutations in MMR (MisMatch Repair) genes. Lynch syndrome (LS) is characterized by a very early onset and lifetime risk estimated to 80%. The gold standard for LS diagnostic is complete Sanger sequencing, a very complex and expensive analysis. MMR mutations are detected in only 60% of criteria fulfilling families, while they are present in up to 20% of families not fulfilling these criteria and which are implicitly excluded from genetic counselling. Therefore, we propose an adapted algorithm, based on germline and tumor analysis, intended to increase molecular diagnostic efficiency and CRC casuistry coverage.

Methods: 20 LS families were selected according to Amsterdam criteria, and one index case per family agreed to participate by signing informed consent. All coding regions and exon-intron boundaries of MSH2, MLH1 and MSH6 were screened by double strand Sanger sequencing. Sequence variants were interpreted by *in-silico* analysis. MLPA was performed for large genomic rearrangements. MMR protein expression in tumors was investigated by immunohistochemistry. Somatic tumor DNA was checked for Microsatellite instability (MSI), MLH1 promoter hypermethylation (PHM), as well as for BRAF V600E mutation.

Results: Over 50% of our samples presented germline variants, the majority being benign. Four unclassified variants are altering splicing enhancers. One deleterious variant, but no recurrent MMR mutations were detected. No large genomic rearrangements were identified. IHC showed loss of MSH2 and MLH1 in several samples also presenting high MSI. No PHM was observed, but somatic BRAF V500E showed to be present in several samples. Data from germline analysis correctly correlated with somatic investigations.

Conclusions: This is the first complete molecular approach of LS in Romania. Our work has an important impact on reducing the cost and time of molecular diagnostic, include for diagnostic more patients than usually selected, perform a more efficient diagnostic with >80% mutation finding probability, provide evidence-based recommendations for oncogenetic diagnostic. Acknowledgement: PN-II-RU-TE-2014-4-2257.

Legal entity responsible for the study: G. T. Popa University of Medicine and Pharmacy, Iasi, Romania

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606P Clinical manifestations and prognostic factors of bone metastasis in colorectal cancer

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Background: Bone metastasis from colorectal cancer (CRC) is known as poor prognostic factor. However, the clinical manifestations and outcomes of CRC with bone metastasis are uncertain.

Methods: CRC with bone metastasis were searched from January 2006 to April 2016, and bone metastasis was diagnosed by plain x-ray, computed tomography (CT), magnetic resonance image (MRI), whole body bone scan (WBBS) or positron emission tomography (PET). Clinical data including site of bone metastasis, visceral metastasis, laboratory finding at diagnosis of bone metastasis, and *K-ras* mutation were reviewed. Time to event endpoint was analyzed by Kaplan-Meier survival curves for overall survival (OS).

Results: Of 12,005 CRC patients, 321 (2.7%) had bone metastasis. Colon cancer (58.5%) is more than rectal cancer (41.5%), and pattern of metachronous bone metastasis was 166 (51.7%). Median time to bone metastasis was 28.2 months from diagnosis of CRC in metachronous patients. The most common bone metastasis site was spine (69.5%) and followed by pelvis (52.1%) and long bone (21.6%). At the time of bone metastasis, liver (58.2%), lung (51.5%) and peritoneal (23.8%) metastasis was also observed, and bone only metastasis was 28 (8.5%) patients. High neutrophil-lymphocyte ratio (NLR, ≥3.0), alkaline phosphatase (ALP, ≥123 IU/L) and carcinoembryonic antigen (CEA, ≥5 ng/mL) had significantly correlated with bone only metastasis at a low frequency. Median OS from diagnosis of bone metastasis was 8.0 months (95% CI = 6.8-9.2). Patients with bone only metastasis had longer OS (median OS, 19.1 vs. 7.6 months, P < 0.001) compared to patients with other organ combined metastasis. On multivariate analysis, age ≥61 (Hazard ratio (HR), 1.35; 95% CI = 1.04-1.74), no bone only metastasis (HR, 2.43; 95% CI = 1.38-4.27), peritoneal metastasis (HR, 1.53; 95% CI = 1.12-2.08), NLR ≥ 3 (HR, 1.49; 95% CI = 1.15-1.95) and ALP ≥ 123 (HR, 1.78; 95% CI = 1.34-2.36) were independent factors for OS. And bone only metastasis is the most significant prognostic factor for bone metastasis of CRC.

Conclusions: Bone metastasis of CRC is not a rare event and has a poor prognosis. Bone only metastasis is the most significant prognostic factor and further studies are needed.

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607P Outcomes of adjuvant chemotherapy for stage II and III colorectal cancer in Korea, 2011-2014: A nationwide study based on the database of quality assessment and the health insurance

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Background: Few population-based analyses on treatment outcomes of colorectal cancer (CRC) have been conducted in Asian countries. We conducted a nationwide study to assess the outcomes of adjuvant chemotherapy (AC) for patients with stage II and III CRC in South Korea.

Methods: Data from the Health Insurance Review and Assessment Service Database (HIRA) were analyzed for demographics, tumor characteristics, adjuvant chemotherapy, and survival of patients who underwent curative-intent surgical resection for CRC from 2011 to 2014.

Results: From the HIRA data, a total of 61315 patients were identified: 15620 (25.5%) in stage I, 20525 (33.5%) in Stage II, and 25170 (41.0%) in stage III. Chemotherapy regimens were consisted: 11332 (18.5%) in 5-fluorouraci plus leucovorin or capecitabine (FL/CAP), 13183 (21.5%) in FL/CAP with oxaliplatin (FOLFOX/CAPOX), 357 (0.6%) in uracil and tegafur/doxifluridine (UFT/D) and 36443 (59.4%) in surgery alone. For the patients with stage II colorectal cancer, the adjuvant chemotherapy was associated with a significant increase in survival rate (FL/CAP: hazard ratio [HR], 0.44; 95% CI, 0.40-0.50, and FOLFOX/CAPOX: HR, 0.48; 95% CI, 0.41-0.55, respectively), however UFT/D regimens were not statistically significant. In the patients with stage III, the adjuvant chemotherapy was significantly effective for survival rate (FL/CAP: HR, 0.43; 95% CI, 0.40-0.47, FOLFOX/CAPOX: HR, 0.38; 95% CI, 0.36-0.41, respectively), UFT/D were also not statistically effective.

Conclusions: Adjuvant chemotherapy with FL/CAP and FOLFOX/CAPOX showed a survival benefit for patients with stage II and III colorectal cancer.

Legal entity responsible for the study: In Gyu Hwang

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Disclosure: All authors have declared no conflicts of interest.

608P Variations in clinicopathological features, treatment patterns, and outcomes of young adults with colorectal cancer in the United States and Egypt

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Background: A recent American Cancer Society study showed that the rate of colorectal cancer (CRC) in young American adults is rising. There are limited data on young Arabian adults with CRC. Herein we explore differences between American and Egyptian young adults with CRC.

Methods: A retrospective review of young (≤46 years old) patients (pts) with CRC in the United States (US-pts) and Egypt (EGY-pts) was undertaken. T and Fisher's exact tests were used for comparative analyses. Kaplan-Meier methodology estimated survival.

Results: In total, 504 pts with CRC were studied, incorporating 62 US-pts (median age 38 yrs, range 20-46) and 442 EGY-pts (35 yrs, 15-46). US-pts were more commonly female (66% vs 41%, $p < 0.001$) and had more colon primaries (75% vs 50%, $p = 0.001$). EGY-pts had more left-sided tumors (78% vs 61%, $p = 0.008$), of which 49% were rectal primaries (vs 24% for US-pts, $p < 0.001$). US-pts had more well-differentiated tumors (25% vs 3%, $p < 0.001$), whereas EGY-pts had more mucin-producing tumors (40% vs 26%, $p = 0.042$). US-pts were more likely to have bowel obstruction (64% vs 17%, $p < 0.001$) and present with metastatic (met) disease (66% vs 28%, $p < 0.001$), particularly in the liver, lung, and peritoneum (56% vs 40%, $p = 0.04$; 35% vs 5%, $p < 0.001$; 48% vs 16%, $p < 0.001$). Comparing pts with met disease, EGY-pts tended to have rectal primaries (33% vs 22%), while US-pts had more right-sided tumors (38% vs 18%). US-pts were more likely to undergo palliative resection or metastatectomy (41% vs 26%, $p = 0.039$) and receive bevacizumab (69% vs 1%, $p < 0.001$). EGY-pts received more 5-FU alone (39% vs 2%, $p < 0.001$) or 5-FU + radiation (40% vs 0%, $p < 0.001$), whereas US-pts received more FOLFOX/FOLFIRI (64% vs 13%, $p < 0.001$). There was no statistically significant difference in median overall survival between US-pts (Not Reached) and EGY-pts (76 months (mos), $p = 0.6$), nor median progression free survival between US-pts (20 mos) and EGY-pts (13 mos, $p = 0.202$).

Conclusions: Significant differences were observed among young US-pts and EGY-pts with CRC, particularly primary tumor location, patterns of metastasis, and treatment used. Further evaluation of the environmental and ethnic impact on disease biology and treatment outcomes is warranted.

Legal entity responsible for the study: Georgetown University IRB

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609TiP PRODIGE 50 - ASPIK French: French double blind randomised study of aspirin versus placebo in resected stage III or high risk stage II colon cancer with PIK3CA mutation

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Background: Four retrospective studies were recently published on aspirin efficacy in patients with surgically resected colorectal cancer (CRC). Two of these studies strongly suggest that low-dose aspirin (100 mg/d) after resection of CRC with *PIK3CA* mutation could act as a targeted therapy with a major protective effect in terms of cancer specific survival. The other two studies did not confirm the benefit of aspirin in this setting. These retrospective studies provide an insufficient level of evidence to demonstrate the benefit of low-dose aspirin as adjuvant therapy for CRC with *PIK3CA* mutation (approximately 12% of all CRC). Therefore, as recommended in the conclusion of these studies and meta-analyses, prospective studies addressing this issue are warranted.

Trial design: PRODIGE 50 is a double blind randomized phase III study comparing aspirin and placebo in patients with curative resection of stage III or high-risk stage II colon cancer with *PIK3CA* mutation. The primary end point is 3-year disease-free survival (DFS). Among secondary endpoints Disease-free survival at 5 years, Overall survival at 5 years, Compliance to aspirin (comptability of containers) will be evaluated. Randomization (1:1 ratio) is stratified according to center, stage (II *vs* III), *RAS* mutation and chemotherapy (oxaliplatin vs no oxaliplatin). The treatment is planned for 3 years (1 tablet 100 mg/day). Abdominal ultrasound/or CT-scan and CEA is performed every 3 to 6 months during 3 years then every 6 months during the two next years. Hypotheses (α two-sided=5%, power= 80%) are to improve 3-year DFS from placebo: 72% to aspirin: 83% (HR = 0.56). 94 events and 264 patients with *PIK3CA* mutation are required. 2200 patients will be screened. Patient blood and tumor tissues will be collected in order to establish a large biobank as a basis for translational research projects including identification and quantification of circulating tumour DNA and evaluating Cox2 expression. Inclusion start is planned on September 2017 until 2019.

Clinical trial identification: NCT02945033

Legal entity responsible for the study: CHU Rouen

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610TiP A randomized Phase 2 study comparing different dosing approaches of induction treatment (first cycle) of regorafenib in metastatic colorectal cancer (mCRC) patients

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Background: Regorafenib is a multikinase inhibitor with broad anti-angiogenic, anti-stroma and anti-proliferative effects that improved overall survival in patients with mCRC after failure of all approved drugs in the CORRECT phase 3 trial. The different tolerability profile of regorafenib compared with other agents normally used for the treatment of colorectal cancer, caused frequent dose-reductions and interruptions, thereby jeopardizing dose-intensity and limiting incorporation of the drug as standard of care. The CORRECT trial showed that the highest rate and intensity of treatment-related adverse events occurs during the first two cycles. The standard approved dose of regorafenib (160 mg daily three weeks on/one week off) was determined in a phase 1 study and this dose was moved directly into the phase 3 trial. The immediate sub-MTD dose level of 120mg daily 3 weeks on/1 week off did not show any DLT among 7 patients treated in the phase I. In addition, an intermittent dose approach consisting of regorafenib 160 mg daily on a 1 week on/1 week off schedule was tested in combination with chemotherapy in the CORDIAL trial and showed a favorable safety profile.

Trial design: This randomized phase 2 study will evaluate the tolerability regorafenib using different dose-escalation approaches in patients with treatment refractory mCRC. Patients will be randomized 1:1:1 to receive regorafenib at the standard approved dose (arm A), or at 120 mg daily 3 weeks on/one week off during the first cycle (arm B), or 160 mg daily one week on/one week off during the first cycle (arm C). In arms B and C, the dose will be escalated to the standard dose from cycle two onwards if no limiting toxicity appears. The primary objective is to compare the safety profile of the different treatment arms. Secondary aims include assessment of the percentage of total administered dose over the planned dose, dose intensity during the treatment period and during first two cycles, disease control rate, progression-free survival, time to treatment failure, and overall survival. The trial is in progress; 160 of 295 planned patients have been recruited at the end of March 2017 (first patient 15 July 2016).

Clinical trial identification: NCT02835924

Legal entity responsible for the study: Spanish Cooperative Group for the Treatment of Digestive Tumors (TTD) in collaboration with UNICANCER GI

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611TiP Nivolumab, ipilimumab and COX2-inhibition in early stage colon cancer

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Background: For the 4% of patients with metastatic mismatch repair deficient (dMMR) colorectal cancers, impressive responses are seen with anti-PD1 monotherapy, with response rates up to 40%. Data in patients with non-metastatic colon cancers (CCs) are lacking. Both MSS and MSI early stage CCs show a higher proportion of T-cell infiltration, when compared to metastatic disease. Also, preclinical work has shown improved responses to anti-PD1 therapy by addition of COX (2)-inhibition, suggesting this could be a useful adjuvant that might help induce responses in MSS CRCs.

Trial design: The NICHE trial is a single center, investigator-initiated study, in which patients with newly diagnosed colon cancer who have no signs of distant metastases will be treated with short-term immunotherapy ± COX2-inhibition. Treatment will be given in the window period until surgical resection of the tumor. In this exploratory study, the primary objective will be to determine the safety and feasibility of pre-operative immunotherapy in CC. Secondary objectives include exploring the immune activating capacity of immunotherapy in early stage CCs and the added effects of COX2 inhibition, changes in immune suppressive pathways and the correlation of mutational load to putative markers of response. After additional tumor biopsies are taken via endoscopy, patients with dMMR tumors will all be treated with a single dose of ipilimumab 1mg/kg on day 1 and two cycles of nivolumab 3mg/kg on day 1 and 15. Patients with MSS tumors will be randomized to receive celecoxib 200mg once daily in combination with abovementioned treatment. After 5-6 weeks, patients will undergo surgery, where tumor and normal tissue will again be harvested. When deemed advisable by the pathology report, standard adjuvant treatment with chemotherapy will be offered. A total of 30 patients with MSS tumors and 30 patients with MSI tumors will be enrolled. Recruitment for this study is ongoing and currently two patients have been enrolled.
Conclusion: This is, to our knowledge, the first study exploring pre-operative immunotherapy in patients with non-metastatic CC and will hopefully help identify mechanisms that interfere with clinical activity of immunotherapy, and to develop future strategies and combinations for CRC.

Clinical trial identification: 2016-002940-17. Release date: January 2017

Legal entity responsible for the study: Netherlands Cancer Institute

Funding: Bristol-Myers-Squibb

Disclosure: D. Cullen: Employment with BMS. J.B. Haanen: Ad board BMS. All other authors have declared no conflicts of interest.

612TiP TRIUMPH Study: A multicenter Phase II study to evaluate efficacy and safety of combination therapy with trastuzumab and pertuzumab in patients with HER2-positive metastatic colorectal cancer (EPOC1602)

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Background: HER2 amplification is identified in approximately 5% out of RAS wild-type metastatic colorectal cancer (mCRC) and likely related to the resistance to EGFR blockade. Some preclinical and clinical studies have shown the efficacy of HER2-targeted therapy against HER2-positive mCRC. To identify this orphan-fractionated mCRC, we collaborate with the nationwide cancer genome screening project (SCRUM-Japan GI-SCREEN) by means of tissue/circulating tumor DNA (ctDNA) screening.

Trial design: TRIUMPH study is a multicenter phase II study to evaluate efficacy and safety of combination therapy with trastuzumab and pertuzumab in patients with HER2-positive mCRC confirmed by either tissue or ctDNA analysis. Eligibility criteria includes histologically confirmed mCRC; ECOG PS $\leq$ 1; RAS wild-type and HER2-positive defined as IHC 3+ or FISH positive (HER2/CEP17 ratio $\geq$ 2.0) by means of tissue screening, or HER2-amplified and RAS wild-type identified from ctDNA (Guardant360); and refractory or intolerant to fluoropyrimidine, irinotecan, oxaliplatin, and anti-EGFR antibody. Enrolled patients will receive intravenous trastuzumab (8 mg/kg loading dose, followed by 6 mg/kg) and pertuzumab (840 mg loading dose, followed by 420 mg) every 3 weeks. In addition, the natural history data of patients with HER2-positive and RAS wild-type who do not meet the eligibility will be followed as a historical control. The primary endpoint is objective response rate (ORR) by investigator's assessment in patients with HER2 positive tumor confirmed by tissue analysis as well as ctDNA analysis, respectively. A sample size for each group is calculated to be 18 on the basis of a power of 80% to test the null hypothesis of ORR of less than 5% versus the alternative hypothesis of ORR of over 30%, at a one-sided alpha level of 0.025. Furthermore, ctDNA will be serially analyzed to investigate the resistance mechanisms; a key focus of current research is to provide clinically meaningful thresholds which may be used for identifying and implementing treatment changes.

Legal entity responsible for the study: Wataru Okamoto

Funding: The Japan Agency for Medical Research and Development

Disclosure: W. Okamoto: Research funding from MSD. Y. Komatsu: Speakers' Bureau: Taiho Pharmaceutical, Lilly, Chugai Pharma, Merck Serono, Novartis, Pfizer, Bayer. Honoraria: Novartis, Pfizer, Bayer. Research funding: Taiho Pharmaceutical, Lilly, MSD, Ono Pharmaceutical, Novartis, Bayer, Chugai Pharma, Yakult. K. Kato: Research funding: ONO, MSD, Shionogi. H. Taniguchi: Honoraria: Chugai Pharma. T. Kato: Speakers' bureau: Chugai Pharmaceutical Co. Ltd., Takeda Pharmaceutical Company Limited, Eli Lilly and Company, Bayer Yakuhin, Ltd., Sanofi S.A., Yakult Honsha Company, Limited. T. Nishina: Honoraria: Chugai Pharmaceutical Co. Ltd. T. Esaki: Honoraria: Chugai, Eli Lilly, Taiho, Merck Serono, Ono, Nihon Kayaku, Eisai. Research funding: Eli Lilly, Taiho, Novartis, Daiichi-Sankyo, DS pharma, AstraZeneca, Merck Serono, Ono, Boehringer, MSD. H. Nomura: Employment: Asahi-Kasei Pharma. A. Ohtsu: Research funding: Bristol-Myers Squibb. T. Yoshino: Research funding: GlaxoSmithKline K.K. and Boehringer-Ingelheim GmbH. All other authors have declared no conflicts of interest.

613TiP Phase II dose titration study of regorafenib for patients with unresectable metastatic colorectal cancer who are progressed after standard chemotherapy

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Background: Developing appropriate therapy for colorectal cancer is one of the most important health issues worldwide. The CORRECT study was a Phase III, international, placebo-controlled study in which the case data was accumulated from 17 countries including Japan. The results showed the overall survival (OS), the primary endpoint, was significantly prolonged in the regorafenib group, compared with the placebo group. A total of 760 patients were enrolled in the CORRECT study, including 100 Japanese patients. On the other hand, the administration method of regorafenib does not depend on the height, weight, or race of the patients, or other parameters, and 160 mg/body/day is the standard starting dose, but some cases require dose reduction to 120 mg/day or less due to the difficulty of continuous administration of 160 mg/day because of adverse events.

Trial design: This is a multicenter, single-arm, phase II trial. Eligibility criteria include age > = 20 years, histopathologically diagnosed colorectal cancer considered as unresectable due to distant metastasis or locally advanced cancer, indicating disease progression during the standard chemotherapy or within three months after the last administration of the standard chemotherapy, with adequate bone marrow reserve and organ function. The standard chemotherapy includes fluoropyrimidine, oxaliplatin, irinotecan, and bevacizumab, and anti-EGFR (incase of patients with only RAS WT). Treatment history of TAS-102 is not allowed. Regorafenib 120 mg/body/day is orally administrated once a day, after meal for 3 weeks (Days 1 to 21), followed by a 1-week treatment-off period (Days 22 to 28). This 4-week period is considered as 1 cycle and shall be repeated until progression of disease based on RECIST v1.1. The purpose of the study is to evaluate the efficacy and safety of regorafenib when starting regorafenib treatment at 120 mg/day for the patients with metastatic colorectal cancer. Primary endpoint: disease control rate (> = 6 weeks). Secondary endpoints: OS, progression-free survival, response rate, safety, and drug adherence.

Legal entity responsible for the study: Toshihiro Kudo

Funding: Bayer Yakuhin, Ltd., Japan.

Disclosure: T. Kudo: I belong to a donated fund laboratory from Yakult Honsha Co., Ltd., Chugai Pharmaceutical Co., Ltd., and Ono Pharmaceutical Co., Ltd. T. Satoh: Honoraria and consulting fee from: Eli Lilly, Chugai, Merck Serono. Research funding (to institution) from: Sanofi, Yakult Honsha, Chugai, Ono. All other authors have declared no conflicts of interest.

614TiP Phase II study of Ccr-based dose-control of S-1 in the first-line chemotherapy of S-1/oxaliplatin (SOX) + bevacizumab regimen for advanced colorectal cancer

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Background: In the 1st line therapy of metastatic colorectal cancer(mCRC), SOX+Bevacizumb(Bev) regimen (L-OHP: 130 mg/m2 day 1, Bev: 7.5 mg/kg day 1, S-1: 80, 100, 120 mg*/body days 1–14 repeated every 3 weeks, *According to body surface area, BSA < 1.25 m2, BSA ≥ 1.25 to < 1.5, BSA ≥ 1.5) has been prooved to be non-inferior to mFOLFOX6+Bev with respcet to PFS by the Japanese phase III study, SOFT trial (JapicCTI-090699). In the east-Asian countries, SOX regimen is now widely used in the 1st line treatment of mCRC because of the advantages of the port-free administration in the out-patient clinic. However, in SOFT trial, incidences of grade 3 or higher diarrhea was statistically higher in SOX group than in mFOLFOX6 group (9% *vs* 3%; p = 0·0040), which was thought to be responsible of S-1. Especially in SOX group, the patients whose creatinine-clearence(Ccr) below 70ml/min, grade 3 or higher diarrhea was significantly by far common than in patients with Ccr above 70ml/min (21.1% vs 5.7%; p = 0.0012). Therefore, it will be suggested that Ccr-based dose-control of S-1 will be effective to decrease severe diarrhea that will lead to the impairment of the compliance of SOX regimen.

Trial design: This trial is an open-label, multi-center, phase 2 study. Before administration of SOX regimen, Ccr is measured. The patients with Ccr >_70, the standard dose will be administered, and in the patients with Ccr 70>_60, the level 1 dose control (decrease) will be performed, and in the patients with Ccr 60>_50, the level 2 dose control will be performed (in the patients <50, no administration will be permitted). The primary endpoint is the incidence of grade 3 or higher diarrhea, and the secondary endpoints are SO, PFS, RR, TTF, R0 resectability, ETS. Thirty-five patients are going to be enrolled, and 21 patients have undergone enrollment at the time of submission of the present abstract.

Clinical trial identification: UMIN000015446

Legal entity responsible for the study: Kyoto Katsura Hospital

Funding: None

Disclosure: All authors have declared no conflicts of interest.

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

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GASTROINTESTINAL TUMOURS, NON-COLORECTAL

616O Pertuzumab (P) + trastuzumab (H) + chemotherapy (CT) for HER2-positive metastatic gastric or gastro-oesophageal junction cancer (mGC/GEJC): Final analysis of a Phase III study (JACOB)

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Background: Targeting HER2 with H + CT significantly improves overall survival (OS) vs CT alone in patients (pts) with HER2-positive mGC/GEJC. In HER2-positive metastatic breast cancer, P + H + docetaxel significantly improves progression-free survival (PFS) and OS vs placebo (PLA) + H + docetaxel. We therefore assessed the efficacy and safety of adding P to H + CT in pts with HER2-positive mGC/GEJC.

Methods: JACOB (NCT01774786) is a double-blind, randomised, PLA-controlled, Phase III study in mGC/GEJC. Pts were randomised 1:1 to PLA + H + CT (standard cisplatin/fluoropyrimidine regimen) or P + H + CT. P and H were given every 3 weeks until disease progression or unacceptable toxicity (P at 840 mg, H: 8 mg/kg loading and 6 mg/kg maintenance doses). CT was given as per standard regimens/doses. Stratification factors were world region, prior gastrectomy and HER2 immunohistochemistry score. Primary endpoint was OS. Secondary endpoints included PFS and safety. JACOB was estimated to have 80% power to detect a significant improvement in OS (hazard ratio [HR] 0.777) at the final efficacy analysis after 502 events (overall two-sided α-level 5%).

Results: From 10 Jun 2013 to 12 Jan 2016, 388 pts were randomised to P + H + CT and 392 to PLA + H + CT. After a median OS follow-up of approx. 2 years, 504 patients had died, 242 in the P + H + CT arm (median OS 17.5 months) and 262 in the PLA + H + CT arm (median OS 14.2 months) (HR 0.84, 95% confidence interval [CI] 0.71–1.00; p = 0.0565). Median PFS was 8.5 months and 7.0 months respectively (HR 0.73, 95% CI 0.62–0.86). The safety profile was generally comparable between treatment arms except for diarrhoea (all grades: 61.6% in P + H + CT vs 35.1% in PLA + H + CT). Incidence of symptomatic and asymptomatic left ventricular systolic dysfunction was low and similar in both arms.

Conclusions: The study failed to demonstrate a statistically significant improvement in OS with the addition of P to H + CT, although a 3.3-month increase in median OS was observed. P was generally well tolerated and no new safety signals were identified. Further analyses will be presented.

Clinical trial identification: Protocol number: BO25114; ClinicalTrials.gov NCT01774786

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

Funding: F. Hoffmann-La Roche Ltd.

Disclosure: J. Tabernero: Advisory board: Amgen, Bayer, Boehringer-Ingelheim, Celgene, Chugai, Genentech, Lilly, MSD, Merck Serono, Novartis, Pfizer, Roche, Sanofi, Symphogen, Taiho, and Takeda. P.M. Hoff: Corporate-sponsored research: Roche. L. Shen: Advisory board: Hengrui, Merck, Roche, BMS. Corporate-sponsored research: Taiho, Hengrui, Merck, Roche AZ. A. Ohtsu: Corporate-sponsored research: BMS. M.A. Shah: Advisory board: Lilly, Inc. Corporate-sponsored research to institution: Roche, Boston Biomedical, Gilead. K. Cheng: Stock ownership: Genentech. Employee of Genentech. C. Song: Stock ownership: Roche. Corporate-sponsored research: Roche. Employee of Roche. H. Wu: Employee of Roche (China) Holding Ltd. J. Eng-Wong: Employee of Genentech. Y-K. Kang: Advisory board: Roche, Novartis, Ono, Daehwa, LSK Biopharma, Blueprint, Taiho, BMS.

617O A Phase 3 Study of nivolumab (Nivo) in previously treated advanced gastric or gastroesophageal junction (G/GEJ) cancer: Updated results and subset analysis by PD-L1 expression (ATTRACTION-02)

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Background: Nivo monotherapy demonstrated its efficacy with manageable safety for G/GEJ cancer refractory or intolerant to standard chemotherapy at the primary analysis (ATTRACTION-02[ONO-4538-12]: ASCO-GI 2017, Kang YK et al. *J Clin Oncol.* 2017; 35 [suppl 4S abstract 2]). Here, we report updated results, and the relationship between efficacy of Nivo and PD-L1 expression levels.

Methods: 493 patients(pts) aged $\geq$ 20 years with ECOG PS 0-1 and unresectable advanced or recurrent G/GEJ cancer after failure of two or more previous chemotherapy regimens were randomized in a 2:1 ratio to receive 3 mg/kg Nivo (N = 330) or placebo (N = 163) every 2 weeks until unacceptable toxicity or disease progression. The primary endpoint was overall survival (OS). The PD-L1 expression was assessed by immunohistochemistry (28-8 pharmDx assay). And updated results of the efficacy and safety were based on $\geq$ 1-year follow-up after last patient enrollment.

Results: As of the data cut-off on February 25th 2017, one year after last patient enrollment, the median OS (mOS) was 5.32 months with Nivo versus 4.14 months with placebo (hazard ratio [HR], 0.61; 95% confidence interval [CI], 0.50-0.75; p < 0.0001). The OS rates were 46.4% (95% CI, 40.8-51.8) versus 34.7% (95% CI, 27.4-42.1) at 6 months and 27.6%(95% CI, 22.8-32.6) versus 11.6% (95% CI,7.2-17.1) at 12 months. Immunohistochemistry was performed for exploratory analyses of OS by PD-L1 status on pretreatment tumor biopsies obtained from 197 pts. In pts with PD-L1-positive (expression $\geq$1%) tumors, the mOS was 5.22 months in the Nivo (16 pts) versus 3.83 months in placebo (10 pts) (HR, 0.58; 95% CI, 0.24-1.38). In pts with PD-L1 negative (<1%) tumors, mOS was 6.05 months (115 pts) versus 4.19 months (52 pts) (HR, 0.70; 95% CI, 0.49-1.00), respectively.

Conclusions: With minimum 1-year of follow-up, long-term survival benefit of nivolumab was confirmed for patients with advanced G/GEJ cancer. Although tumor samples were available only in 40% of all enrolled patients, Nivo demonstrated benefit irrespective of PD-L1 expression in the exploratory analysis.

Clinical trial identification: NCT02267343

Legal entity responsible for the study: Ono Pharmaceutical Co., Ltd

Funding: Ono Pharmaceutical Co., Ltd, Bristol-Myers Squibb

Disclosure: N. Boku: Ono, Taiho, Chugai, Eli-Lilly. Y-K. Kang: Ono, Bristol-Myers Squibb, Lilly/ImClone, Taiho Pharmaceutical, Roche/Genentech, Novartis, Bayer. T. Satoh: Ono. K. Kato: Ono, Shionogi, MSD. H.C. Chung: Lilly, GSK, MSD, Merck Serono, BMS, Ono, Taiho, Celltrion, Quintiles, BMS. K. Muro: Shionogi, MSD K.K., Daiichi Sankyo, Kyowa Hakko Kirin, Gilead Sciences, Chugai, Takeda, Eli Lilly Japan K.K., Merck Serono, Taiho, Yakult Honsha. T. Yoshikawa: Taiho, Chugai, Yakult, Ono, MSD. K-W. Lee: Ono. L-T. Chen: Ono, Eli-Lilly, MSD, PharmaEngine, Merrimack, TTY, Syncore, Five Prime, Novartis, GSK, Merck Serono, Polaris, Anti-Alpha Enolase (ENO-1) monoclonal antibody/HuniLife. All other authors have declared no conflicts of interest.

618O Health-related quality of Life (HRQOL) and disease symptoms in patients with unresectable hepatocellular carcinoma (HCC) treated with lenvatinib (LEN) or sorafenib (SOR)

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Background: A recent phase 3, randomized, open-label, noninferiority trial compared the efficacy and safety of LEN to SOR as first-line systemic treatment in unresectable HCC (954 patients). The study included analyses to evaluate the impact of therapy for HCC on HRQOL.

Methods: HRQOL was assessed using the European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire (EORTC QLQ-C30), the HCC-specific module (EORTC QLQ-HCC18), and the European Quality of Life (EQ-5D-3L) at baseline, Day 1 of each cycle, and off-treatment visit. Changes from baseline in both treatment arms were assessed using linear-mixed models with selected covariates (baseline score, geographical region, macroscopic portal vein invasion and/or extrahepatic spread, ECOG-PS, body weight). Time to worsening for each domain was represented as months to deterioration defined by a minimally important difference (MID).

Results: A total of 954 patients (LEN treatment n = 478; SOR treatment n = 476) were randomized and included in the intent-to-treat population. Baseline HRQOL scores were similar for patients receiving LEN or SOR across all domains. Significant changes from baseline HRQOL scores were noted for Nutrition, Diarrhea, Role Function (RF), Pain, and Body Image (BI). In the QLQ-HCC18 Nutrition domain, lower adjusted mean scores in favor of LEN were reported at most time points with significant differences at Cycle 6 and Cycle 9 ($p < 0.05$). SOR was associated with worsening Diarrhea symptoms with lower adjusted mean scores in favor of LEN reported at Cycles 3, 6, 9, and 12 ($p < 0.01$). Median months to clinically meaningful worsening among each treatment group was statistically significant favoring LEN for the QLQ-C30 domains of RF (2.0 vs 1.9; $p = 0.0098$), Pain (2.0 vs 1.8; $p = 0.0060$), and Diarrhea (4.6 vs 2.7; $p < 0.0001$), and in the QLQ-HCC18 domains of BI (2.8 vs 1.9; $p = 0.0041$), and Nutrition (4.1 vs 2.8; $p = 0.0060$).

Conclusions: Most domains met the noninferiority assumption between LEN and SOR. The additional evidence of significant HRQOL benefits further support LEN in terms of functional deterioration delays.

Clinical trial identification: NCT01761266

Legal entity responsible for the study: Eisai Inc

Funding: Eisai Inc

Disclosure: M. Kudo: Honoraria: Bayer, Eisai, MSD, EA Pharma. S. Hudgens: Consultant to Eisai. J-H. Yoon: Research grants from Bayer HealthCare Pharmaceuticals, Daewoong Pharmaceuticals, and Bukwang Pharmaceuticals. C. López López: Grants, personal fees, non-financial support and other from Eisai, Bayer, Lilly, Daiichi Sankyo. C. Dutcus: Employee of Eisai Inc. S. Kraljevic: Employee of Eisai Co Ltd. T. Tamai, G. Meier: Employee of Eisai Inc. V. Breder: Consulting: BMS, MSD, Bayer, Boehringer-Ingelheim. Lectures: BMS, MSD, Bayer, Boehringer-Ingelheim. All other authors have declared no conflicts of interest.

619O JET-HCC: A phase 3 randomized, double-blind, placebo-controlled study of tivantinib as a second-line therapy in patients with c-Met high hepatocellular carcinoma

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Background: Tivantinib is a small molecule inhibitor of c-Met. A previous phase 2 study suggested a clinical benefit of tivantinib as a second-line therapy for hepatocellular carcinoma (HCC) with high expression of c-Met. This Japanese study aimed to confirm the efficacy and safety of tivantinib in this population (NCT02029157).

Methods: Main inclusion criteria were HCC patients refractory or intolerant to a prior sorafenib therapy, Child Pugh A, ECOG PS ≤ 1, at least one measurable lesion according to RECIST 1.1, and diagnosed as c-Met high (regarded as $\geq 2+$ in $\geq 50\%$ of tumor cells, by IHC). Enrolled patients were blindly randomized to either tivantinib or placebo group in 2:1 ratio. Stratification factors were vascular invasion (Y/N) and ECOG PS (0/1). Tivantinib (120 mg bid) or placebo was orally administered until discontinuation criteria was met. Primary endpoint was PFS by the independent review committee, based on CT/MRI every 6 weeks. Secondary endpoints included OS and safety. A sample size of 160 patients and 136 PFS events were calculated to detect a HR of 0.6 (improvement in median PFS from 8 to 13.3 weeks), with 10% dropout, 80% power, and log-rank test with 5% two-sided alpha.

Results: From 60 sites in Japan, 386 patients were consented, and 195 patients were randomized (tivantinib; n = 134, placebo; n = 61). As results, median PFS was 2.8 months in the tivantinib group, whereas 2.3 months in the placebo group (HR = 0.72 [95% CI 0.51-1.02], $p = 0.065$). Median OS at the time of analysis was 9.9 months in the tivantinib group, whereas 8.5 months in the placebo group (HR = 0.85 [95% CI 0.59-1.22]), but additional follow up may be needed to confirm long-term outcome. Grade ≥ 3 AE occurring $\geq 5\%$ were neutropenia (31.6%), leukopenia (24.8%), lymphopenia (7.5%), anemia (14.3%) and febrile neutropenia (6.0%) in the tivantinib group, whereas none in the placebo group. New toxic profile was not identified except for known AE in the previous study.

Conclusions: Although favorable survival were observed in the tivantinib group, this study in Japan could not show the significant clinical benefit of tivantinib as a second-line therapy for c-Met high HCC.

Clinical trial identification: NCT02029157

Legal entity responsible for the study: Kyowa Hakko Kirin

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620PD YOSEMITE: A 3 arm double-blind randomized phase 2 study of gemcitabine, paclitaxel protein-bound particles for injectable suspension, and placebo (GAP) versus gemcitabine, paclitaxel protein-bound particles for injectable suspension and either 1 or 2 truncated courses of demcizumab (GAD)

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Background: Delta-like ligand 4 (DLL4) is a ligand that activates the Notch pathway which is important for cancer stem cell (CSC) survival. Demcizumab is a humanized, anti-DLL4 antibody that has been shown using an in vivo tumorigenicity limiting dilution assay to inhibit tumor growth and decrease CSC frequency in minimally passaged human xenograft models. In addition, inhibition of DLL4 has also been shown in preclinical studies to cause dysfunctional sprouting of new vessels resulting in an antiangiogenic effect. Encouraging data from a Phase 1b study of paclitaxel protein-bound particles for injectable suspension (Abraxane®), gemcitabine and demcizumab in patients with 1st line metastatic pancreatic cancer led to this double blind randomized 3 arm placebo-controlled Phase 2 study.

Methods: Patients with metastatic pancreatic cancer were randomized (1:1:1) to 1st-line therapy with either Arm 1 - GAP, Arm 2 - GAD with a single 70 day truncated course of demcizumab or Arm 3 - GAD with two 70 day truncated courses of demcizumab (second course starting on Day 168). GA were given at usual dose & schedule, P/D was given IV on days 1 and 15 in cycles 1-3 & 7-9. The primary endpoint was progression-free survival and secondary endpoints included response, survival, safety, immunogenicity, pharmacokinetics, and biomarkers of Notch signaling and CSCs in blood, hair follicles and tumor cells. The primary study analyses compared GAP to the two pooled GAD arms.

Results: 207 patients were randomized and 204 were treated. The median age was 63, the male/female ratio was 116/88, the ECOG 0 vs 1 distribution was 98/106, the median # metastatic sites was 2 and 74% had hepatic metastases. The response/clinical benefit rates were 41.2%/70.6% and 33.1%/74.3% in the GAP and pooled GAD arms, respectively. The median progression-free survival (PFS) (mPFS) was 5.5 months in the GAP and pooled GAD arms. The interim median overall survival (OS) for the GAP and pooled GAD arms were not reached and 13.2 months (HR = 1.02), respectively. Geographic differences in OS were observed. GAD was generally well tolerated with nausea, diarrhea, anemia, peripheral edema and fatigue being the most common reported toxicities. The incidence of the Grade 3 or greater toxicities of special interest with demcizumab therapy were hypertension (7.4% vs 16.2%), pulmonary hypertension (0% vs 0.7%), heart failure (0% vs. 3.7%), and bleeding (1.5% vs. 8.1%) in the GAP and pooled GAD arms, respectively. No cases of Grade 3 heart failure or pulmonary hypertension occurred during the 2nd 70 day course of demcizumab.

Conclusions: The addition of either 1 or 2 truncated courses of demcizumab to 1st-line gemcitabine and Abraxane did not improve the efficacy compared to GAP in patients with 1st line metastatic pancreatic cancer. GAD therapy was generally well tolerated.

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Legal entity responsible for the study: OncoMed Pharmaceuticals

Funding: OncoMed Pharmaceuticals

Disclosure: R. Stagg: Employee and own stock of OncoMed. All other authors have declared no conflicts of interest.

621PD A Phase 2b of eryaspase in combination with gemcitabine or FOLFOX as second-line therapy in patients with metastatic pancreatic adenocarcinoma (NCT02195180)

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Background: L-asparaginase (L-ASP) hydrolyses asparagine, an amino acid essential for the survival and proliferation of cancer cells. Asparagine synthetase (ASNS) expression is believed to play a role in determining sensitivity to asparaginase treatment. Eryaspase, L-ASP encapsulated in erythrocytes, showed encouraging activity and improved safety profile compared to L-ASP in patients (pts) with relapsed ALL. This prompted us to evaluate eryaspase in combination with chemo in pancreatic cancer (PC).

Methods: This open label, multicenter phase 2b randomized study (2:1) enrolled pts with second-line metastatic PC. Pts eligible to gemcitabine or FOLFOX regimen were randomized to chemo +/- eryaspase (100 IU/Kg D3 and D17 of 4-wk regimen) until disease progression. The endpoint of the study was improvement in PFS or OS in pts with no or low ASNS (0/1) expression as determined by IHC, with a target Hazard ratio (HR) < 0.85. Secondary endpoints included OS, PFS, ORR, safety and QoL. The primary analysis took place after around 6 mo follow-up (FUP).

Results: 140 pts were enrolled. The baseline characteristics were well balanced across the 2 treatment arms. The ASNS 0/1 (n = 65 and 32 in eryaspase & control arms, respectively), demonstrated a HR of 0.73 for PFS and 0.62 for OS; therefore the trial met its primary endpoint. In the entire patient population, eryaspase led to improvement of OS (median 26.1 wks) compared to control (median 19 wks); HR of 0.57 (P = 0.03). Similarly, eryaspase led to significant improvement in PFS. The treatment effect in favor of eryaspase was comparable across various prognostic indicators. Overall, treatment was well tolerated, with asthenia, nausea and vomiting, and myelosuppression being the most frequent events in both arms. Final results with additional FUP on efficacy and safety outcome measures will be provided at the meeting.

Conclusions: In pts with PC receiving second-line chemotherapy treatment, the addition of eryaspase provided significant improvement in OS and PFS, irrespective of ASNS expression levels. The role of the ASNS expression will be further investigated. Further investigation of eryaspase in PC in a P3 study is warranted.

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Legal entity responsible for the study: Erytech Pharma

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622PD nab-Paclitaxel (nab-P) plus gemcitabine (G) for patients (Pts) with locally advanced pancreatic cancer (LAPC): Interim efficacy and safety results from the Phase 2 LAPACT Trial

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Background: Treatment options for pts with LAPC are limited. In the phase 3 MPACT trial, *nab*-P + G treatment (Tx) resulted in a > 3-fold reduction in primary pancreatic tumor burden vs G in pts with metastatic PC, suggesting that the regimen may be effective in LAPC. Interim efficacy and safety results from the international, multicenter, prospective phase 2 LAPACT trial are presented.

Methods: During induction, treatment-naive pts with unresectable LAPC and ECOG PS ≤ 1 received 6 cycles of *nab*-P 125 mg/m^2 + G 1000 mg/m^2 on D 1, 8, and 15 of each 28-day cycle. After induction, pts without PD or unacceptable AEs were eligible for the investigator's choice (IC) of continued Tx with *nab*-P + G, chemoradiation (CRT), or surgery. Surgery could occur prior to completing 6 cycles if the investigator deemed a sufficient tumor response. The primary endpoint was TTF. A secondary endpoint was disease control rate (DCR = CR, PR, and SD [≥ 16 weeks]) in pts who completed induction and had ≥ 1 postbaseline assessment. Data for pts who received their first dose of Tx by Oct 1, 2016 are reported.

Results: A total of 101 pts with LAPC received *nab*-P + G induction. Median age was 65 years (range, 42-85), and median time from primary diagnosis to first dose was 27 days. Pts received a median of 5 Tx cycles (range, 1-6). A total of 60 patients (59%) completed induction. Among 93 evaluable patients, the DCR was 82% (76/93; PR, n = 33; SD ≥ 16 wks, n = 43); 12 pts had SD < 16 wks, and 5 pts (5%) had PD. The most frequent reasons for discontinuation during induction (n = 101 evaluable) were AEs (18%), PD (7%), and physician decision (5%). The 2 most common grade ≥ 3 AEs were neutropenia (37%) and anemia (9%). Grade ≥ 3 peripheral sensory neuropathy was reported in 4% of pts. After completion of induction, 42 patients received protocol-specific IC therapy: 13 continued *nab*-P + G, 15 received CRT, and 14 underwent surgery (R0, n = 4; R1, n = 6; R2, n = 1; 3 missing; resection conversion rate = 33%).

Conclusions: The reported DCR of 82% and PR rate of 35% for *nab*-P + G are promising, and there were no new safety signals compared with previous studies. These interim results suggest that *nab*-P + G is an appropriate LAPC Tx. NCT02301143.

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Legal entity responsible for the study: Celgene Corporation

Funding: Celgene Corporation

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623PD A phase I and randomized phase II trial to evaluate the efficacy and safety of nab-paclitaxel (nab-P) in combination with gemcitabine (G) for the treatment of patients with ECOG 2 advanced pancreatic cancer (PDAC)

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Background: Nab-P+G significantly improved overall survival versus G in Patients (P) with Karnofsky index ≥70% metastatic PDAC (Von Hoff et al, 2013). The aim of this study was to select a tolerable dose -schedule of nab-P+G (Ph I), and to evaluate the efficacy of the selected regimen (Ph II) in patients with previously untreated ECOG-2 advanced PDAC.

Methods: In the phase1 portion of the study patients were randomized to one of 4 treatment regimens including G 1000 mg/m^2 and nab-P 150 mg/m^2 (arm B) or 125 mg/m^2 (arm D) days 1 and 15 every 28 days or same dose of G and nab-P 100 mg/m^2 (arm C) or 125 mg/m^2 (arm E) days 1, 8, and 15 every 28 days. The two safest regimens determined by analyzing hematological and non-hematological grade 3-4 toxicity, 30 and 60 days mortality, treatment discontinuation due to toxicity and dose intensity were selected for evaluation in the phase 2 portion of the study with 6 months overall survival (OS) as the primary endpoint.

Results: Regimens arm C and arm E (days 1, 8, 15 every 28 days schedule) were selected for the phase 2 portion of the study. A total of 221 patients (111 in arm C/110 in arm E) were enrolled. Median age was 71/68 y, 51/55% were male and 91/83% had metastatic disease (liver 63/62%). Most frequent grade 3-4 toxicity per arm were anemia (12/7%), neutropenia (32/30%), thrombocytopenia (7/11%), febrile neutropenia (3/4%), asthenia (14/16%) and neurotoxicity (11/16%). There were no significant differences in 6 months OS 63/69%, response rate (RR) 24/28% and median progression free survival (PFS) 5.7/6.7 months respectively in each arm.

Conclusions: Nab-P in combination with G, both at 100 and 125 mg/m^2 dose administered on a standard schedule of days 1, 8 and 15 is well tolerated and results in acceptable OS, RR and PFS in this fragile patient population.

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Legal entity responsible for the study: PH Research

Funding: Celgene

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624PD A phase III trial of muparfostat (PI-88) as adjuvant therapy in patients with hepatitis virus related hepatocellular carcinoma (HV-HCC) after resection

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Background: Muparfostat is an investigational new drug which deters tumor growth by blocking tumor angiogenesis and prevents tumor cells from spreading via heparanase inhibition. Previous phase II trial of muparfostat demonstrated good tolerability and favorable clinical response.

Methods: This international multicenter clinical trial was conducted in Asia-Pacific region (Taiwan, Korea, China, and Hong-Kong) from 2011. A total of 520 HV-HCC patients after surgical resection were randomized (1:1) to receive injection of either muparfostat (160 mg/day, 4-days-on/3-days-off, 3-weeks-on/1-week-off) or placebo for 52 weeks and followed up for 96 weeks. The primary endpoint was centrally assessed disease-free survival (DFS). Secondary endpoints included overall survival (OS), time to recurrence, and safety.

Results: Baseline patient demographics and characteristics were balanced between the treatment and placebo arms. All subjects completed the 52-week treatment. After interim analysis in 2014, the trial was concluded in 2015. The final intention-to-treat analysis ($N = 519$) yielded a non-significant result ($p > 0.05$) on DFS, not reaching the primary end point. Nevertheless, per-protocol analysis ($N = 423$) revealed a possible positive protective effect in subgroup patients with microvascular invasion. Muparfostat showed a significant prolongation in the disease-free time after completion of the 1-year treatment (hazard ratio: 0.13, 95% CI: 0.017 - 0.991, $p = 0.049$). Muparfostat had a good safety profile. There were five clinically suspected cases of heparin-induced thrombocytopenia but only one was confirmed.

Conclusions: Despite the DFS was not improved in the overall treatment group, muparfostat could significantly prolong the DFS in the microvascular-invasion subgroup, comprising 40% of the trial population. The finding potentiated muparfostat as single therapy or in combination with other anti-cancer agents for future HCC adjuvant therapy trials.

Clinical trial identification: PATRON/NCT01402908

Legal entity responsible for the study: Medigen Biotechnology Corporation

Funding: Medigen Biotechnology Corporation

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625PD Protein biomarkers as predictors of outcome with regorafenib (REG) in patients (pts) with hepatocellular carcinoma (HCC) in the RESORCE trial

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Background: REG improved overall survival (OS) and time to progression (TTP) versus placebo in pts with HCC who progressed during prior sorafenib in the phase 3 RESORCE trial. This exploratory analysis evaluated potential correlations between baseline plasma protein levels and REG clinical benefit (OS and TTP) in RESORCE.

Methods: Baseline plasma samples were available from 499/573 pts. A total of 266 circulating proteins valid for analysis were quantified by a Luminex assay (Myriad RBM). The predictive and prognostic effects (HR and 95% CI) were evaluated using a Cox proportional hazards model with protein levels measured as a continuous variable. The predictive effect was modeled as a protein–treatment interaction effect and subjected to Akaike information criterion (AIC)-based selection to assess its association with OS and TTP. Subgroup analysis was done on proteins identified as significant for OS and TTP to generate a patient-wise protein composite score.

Results: The overall and biomarker cohorts were similar for demographic variables and outcomes. Five proteins were predictive for OS (Table), but were not prognostic; 47 were predictive for TTP (6 were prognostic) and included the 5 proteins predictive for OS. In general, the REG treatment benefit for OS was maintained in dichotomized, quartile, and STEPP subgroup analyses, with lower protein levels correlating with improved treatment benefit. However, composite scores integrating information across predictive proteins indicated that in a small group of pts ($n = 20$ OS; $n = 8$ TTP) a high protein concentration was associated with a reduced treatment effect.

Conclusions: Although this exploratory analysis suggests that most pts with HCC derive benefit from REG treatment, multiple proteins were identified as potentially predictive for OS and TTP treatment benefit with REG. Further analyses including biochemical and clinical factors are warranted.

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Legal entity responsible for the study: Bayer

Funding: Bayer

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Table: 625PD

Protein	REG-predictive effect on OS, HR (95% CI)	Interaction P-value	Adjusted interaction P-value	Reference
LOX-1	1.35 (1.16, 1.57)	<0.001	0.009	1 ng/mL increase
ANG-1	1.12 (1.05, 1.19)	<0.001	0.019	1 ng/mL increase
Cystatin-B	1.46 (1.15, 1.85)	0.002	0.040	2-fold increase
LAP TGF-beta 1	1.36 (1.12, 1.65)	0.002	0.040	2-fold increase
MIP-1alpha	1.02 (1.01, 1.04)	0.002	0.040	1 pg/mL increase

626PD A randomized phase III trial comparing 4 courses and 8 courses of S-1 adjuvant chemotherapy for p-stage II gastric cancer: JCOG1104 (OPAS-1)

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Background: Postoperative S-1 for 1 year (corresponding to 8 courses) is a standard adjuvant chemotherapy for p-stage II gastric cancer based on ACTS-GC phase III study comparing surgery alone and S-1. Duration of adjuvant chemotherapy for 1 year selected in ACTS-GC was not based on solid evidence while 6 months are established for colon cancer based on several phase III studies to compare duration. It remains unclear whether S-1 for 1 year could be shortened to 6 months (corresponding to 4 courses) without worsening the survival.

Methods: We conducted a multi-center phase III trial to confirm non-inferiority in relapse-free survival (RFS) of 4 courses S-1 to 8 courses S-1 in p-stage II gastric cancer. Key eligibility criteria were p-stage II except T1 and T3N0 (7th edition of TNM), performance status 0-1, R0 resection with D2 lymph node dissection for $\geq$c-stage II or D1+ lymph node dissection for c-stage I, within 7 weeks after surgery, and age between 20 and 80 years. Primary endpoint was RFS and secondary endpoints included overall survival (OS), time to treatment failure (TTF), and adverse events. Patients were randomized into 4 course S-1 or 8 courses S-1. 80 mg/m^2 of S-1 was administered for 4 weeks with a rest for 2 weeks as one course. Total sample size was determined to be 1,000 with 3-year RFS of 85% in both arms and non-inferiority margin of hazard ratio (HR) of 1.37, one-sided alpha of 5% and 80% power.

Results: Between Feb 2012 and Mar 2017, 590 patients were enrolled in this study. Among them, 528 patients were analyzed at the first planned interim analysis at Mar 2017. JCOG Data and Safety Monitoring Committee recommended early termination of the trial because the point estimate of HR was greater than non-inferiority margin of HR, which met the prespecified criteria for early stopping. The study was closed on the basis of futility. RFS at 3 years was 88.9% for 4-courses arm and 95.3% for 8-courses arm (HR 2.52, 95% CI 1.11-5.77). OS at 3 years was 91.7% for 4-courses arm and 97.7% for the 8-courses arm (HR 5.18, 95% CI 1.50-17.89).

Conclusions: Postoperative S-1 adjuvant chemotherapy for p-stage II gastric cancer should be continued until 1 year so far as feasible.

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Legal entity responsible for the study: Japan Clinical Oncology Group (JCOG)

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Disclosure: T. Yoshikawa, N. Boku, M. Sasako: Lecture fee from Taiho, Eli Lilly, and Chugai Pharmaceutical. M. Terashima, H. Yabusaki, S. Ito, T. Sano: Lecture fee from Taiho. H. Fukuda: Lecture fee from Taiho Pharma, Chugai Pharmaceutical. All other authors have declared no conflicts of interest.

627PD Comparison of the eighth and seventh editions of the American Joint Committee on Cancer TNM staging systems for gastric cancer: Proposal for a simplified and improved TNM staging system

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Background: To evaluate the prognostic significance of the eighth edition of American Joint Committee on Cancer (AJCC) TNM staging classification for gastric cancer.

Methods: Data from 4,957 consecutive patients who underwent radical gastrectomy between 1997 and 2014 were retrieved from our database. The prognostic value of the eighth edition was compared with that of the seventh edition of the AJCC TNM classification. The analysis was repeated in an external validation set.

Results: Significant differences in 5-year overall survival (OS) rates were observed for each TNM stage when using the eighth edition system, and smaller AIC values and a higher c-statistic were observed relative to those of the seventh edition. However, the OS rates in each subgroup of stage III patients in the eighth edition were significantly different. Additionally, patients with the same pN stage, namely the pT4a and pT4b groups, showed similar 5-year OS. Based on the survival data, we propose a simplified staging system. In the improved TNM (iTNM) staging system, the subgroups of a given TNM stage do not have statistically significant OS differences. The iTNM staging exhibits superior prognostic stratification, with lower AIC values and a higher c-statistic than the eighth edition TNM classification. Similar results were obtained with the external validation dataset.

Conclusions: The eighth edition of the AJCC TNM classification provides superior prognosis to that of the seventh edition. However, it remains associated with some stage migration. The iTNM staging system permits simplification and slightly better prognostic prediction.

Legal entity responsible for the study: Changming Huang

Funding: None

Disclosure: All authors have declared no conflicts of interest.

628P Treatment outcome of gastric cancer associated with esophageal cancer

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Background: The incidence of synchronous and metachronous gastric cancer is high in esophageal cancer patients.

Methods: 113 esophageal cancer (EC) patients with synchronous and metachronous gastric cancer (GC) were analyzed between 1997 and 2016 retrospectively. There were 110 men and 3 women, with a median age of 67 years. 58 had a synchronous gastric cancer (S group) and 55 had a metachronous (M group). In the M group, there were 36 patients with a subsequent esophageal cancer (SEC) and 19 with an antecedent esophageal cancer (AEC).

Results: 1) S group: T stage of EC was 1 in 14 patients, 2 in 4, 3 in 25, and 4 in 15. Stage was 0 in 4 patients, I in 6, II in 9, and III in 39. T stage of GC was 1 in 46 patients, 2 in 6, 3 in 4, and 4 in 2. Stage was I in 49 patients, II in 5, and III in 4. 35 underwent esophagectomy (31 gastrectomy and 4 endoscopic treatments) and 23 received definitive chemoradiotherapy for EC (4 gastrectomy, 3 endoscopic treatments, and 16 observations for gastric cancer). 2) SEC group: The median range between gastrectomy and esophageal treatment was 8.4 years. T stage of EC was 1 in 13 patients, 2 in 6, 3 in 11, and 4 in 6. Stage was I in 3 patients, II in 8, and III in 25. Of the 36 pts, 16 underwent esophagectomy, 18 received definitive (chemo-) radiotherapy, and 2 underwent endoscopic treatment. 3) AEC group: The median range between esophagectomy and gastric treatment was 6.5 years. T stage of EC was 1 in 6 patients, 2 in 1, and 3 in 8, and 4 in 4. Stage was I in 6, II in 6, and III in 7. T stage of GC was 1 in 11 patients, 2 in 4, and 3 in 4. Of 19, 10 underwent endoscopic treatment, 5 underwent gastrectomy, 1 received chemotherapy, and 1 did not receive any anti-cancer treatment. The overall survival rates at 5 years in S group, SEC group, and AEC group were 50%, 45%, and 51%, respectively. There was a significant difference in the overall survival rates between the surgery group (45%) and non-surgery group (36%) in the S group ($p = 0.0006$). In the SEC group, there was a tendency of long survival in those who underwent surgery (56%), compared to those who did not have surgery (37%) ($p = 0.06$). Prognosis of patients with gastric tube cancer was 10 years after EC treatment and 4 years after gastric tube cancer treatment.

Conclusions: Patients in the S group who underwent surgery had a good prognosis. Periodic endoscopic examination is necessary for early diagnosis of gastric tube cancer.

Legal entity responsible for the study: Kurume University School of Medicine

Funding: None

Disclosure: All authors have declared no conflicts of interest.

629P Sarcopenia, myosteatosis, and weight loss as determinants of survival and toxicity in patients with resectable esophageal and gastroesophageal junction (GEJ) cancer receiving preoperative chemoradiotherapy (CRT)

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Background: Abnormal body composition (sarcopenia, myosteatosis, and significant weight loss of $\geq$ 8% (SWL)) has been associated with poor outcomes. This study evaluated sarcopenia, low skeletal muscle attenuation (SMA), and SWL as factors associated with toxicity, recurrence free survival (RFS), and overall survival (OS) with neoadjuvant CRT, in patients with resectable esophageal/GEJ cancer.

Methods: We retrospectively reviewed all pts with resectable esophageal/GEJ cancer treated with curative intent preoperative CRT (paclitaxel/carboplatin) from 2010-2013. Pretreatment CT scans were used to measure skeletal muscle index (SMI) and SMA to determine sarcopenia and myosteatosis, respectively. SWL was determined from the first dietitian recorded body weight and pre-morbid body weight. Treatment delays/modifications (TDM) were used as surrogates for toxicity.

Table: 629P Body composition analysis, toxicities, and OS

		SMI		SMA		Weight Loss	
	All Patients	Sarcopenia n = 35 (40%)	No Sarcopenia n = 53 (60%)	Myosteatosis n = 46 (52%)	No Myosteatosis n = 42 (48%)	SWL n = 40 (45%)	Non-SWL n = 48 (55%)
Mean SMI (cm^2/m^2)	51.2	44.1	55.9	49.3	53.4	47.9	54.0
Mean MA (HU)	34.2	33.6	34.6	27.9	41.0	33.1	35.0
Mean Weight Loss (%)	9.0	10.2	8.2	10.5	7.4	16.2	3.1
Treatment delays/modifications							
YES	36 (40.9%)	13 (37.1%)	23 (43.4%)	26 (56.5%)	10 (23.8%)	21 (52.5%)	15 (31.3%)
NO	52 (59.1%)	22 (62.9%)	30 (56.6%)	20 (43.5%)	32 (76.2%)	19 (47.5%)	33 (68.8%)
Median OS (months)	23.4	19.8	28.3	20.3	28.3	16.7	49.4

Results: Of 88 evaluable patients, 76 (86%) were males with a median age of 62. Histology includes: 72 (82%) adenocarcinoma; 13 (15%) squamous cell carcinoma, 3 (3%) other. Sarcopenia, myosteatosis, and SWL were present in 35 (40%), 46 (52%) and 40 (45%) patients, respectively. By univariate analysis, sarcopenia and SWL were associated with shorter OS and RFS (Sarcopenia $p = 0.009$ and $p = 0.042$, respectively, SWL $p = 0.012$ and $p = 0.061$, respectively). Myosteatosis was associated with TDM ($p = 0.001$). On multivariate analysis, sarcopenia and SWL were associated with shorter OS and RFS, independent of stage and performance status (PS).

Conclusions: Sarcopenia and SWL are associated with shorter OS and RFS independent of stage and PS. Myosteatosis is associated with treatment-related toxicities. These results highlight the prognostic and predictive utility of body composition analysis in survival and treatment related toxicities in esophageal/GEJ cancer patients treated with curative intent preoperative CRT.

Legal entity responsible for the study: Arthur Lui

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630P Optimal extent of abdominal lymph node dissection for advanced Siewert type II and III esophagogastric junction carcinoma

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Background: The aim of this study was to clarify the optimal abdominal lymphadenectomy for advanced in Siewert types II and III adenocarcinoma of the esophagogastric junction (AEG).

Methods: From June 2007 to June 2014, the data of 573 patients who underwent radical total gastrectomy due to advanced Siewert types II and III was collected and retrospectively analyzed. The incidence of abdominal lymph node metastasis (LNM) of each station were compared between patients with Siewert type II and III AEG. And we used the therapeutic index to assess the efficacy of abdominal lymph node dissection of each station.

Results: Of the 573 patients, 247 (44.0%) had Siewert type II AEG and 326 (56.0%) had type III AEG. Among them, 252 patients carried out abdominal D2 lymphadenectomy and 321 patients underwent D2 lymphadenectomy without No. 10 lymphadenectomy (D2-). The mean number of dissected LNs was 34.6 ± 13.0, and the numbers of dissected lymph nodes at each lymph node station did not significantly differ between patients with type II and III AEG ($P > 0.05$). The therapeutic index of No.1-3, 7, 9 and 11 LNs was over 4.0 in advanced type II AEG cases, while the index was higher than 4.0 in No.1-4 and 7-11 LNs in patients with type III AEG. The index of No.10 LNs was more than 10 in type III AEG subgroups with primary tumors invading the serosa layer (15.6), undifferentiated cancers (10.9) and tumor size ≥50mm (10.5).

Conclusions: Dissection of No. 1-3, 7, 9 and 11 LNs would obtain highest survival benefits regardless of the Siewert subtype. Patients with type AEG, especially those with primary tumors invading the serosa layer, undifferentiated cancers and tumor size ≥50mm might obtain relatively higher survival benefits from No. 10 lymphadenectomy.

Legal entity responsible for the study: Changming Huang

Funding: None

Disclosure: All authors have declared no conflicts of interest.

631P Prognostic stratification of pathologic stage in patients with preoperative chemoradiotherapy followed by curative esophagectomy for localized esophageal squamous cell carcinoma

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Background: While the majority of advanced-stage esophageal cancers are treated with surgery after neoadjuvant chemoradiotherapy (NCRT), the utility of prognostication of pathologic TNM stage (pTNM) after NCRT (ypTNM) remains elucidated. Since ypTNM stage could be influenced by pretreatment tumor burden or treatment efficacy of NCRT, ypTNM stage-specific groups might be heterogeneous in terms of prognosis. Identifying prognostic factors in ypTNM stage-specific groups would guide more detailed prognostication.

Methods: From 2007 to 2014, 569 patients with squamous cell carcinoma who underwent R0 surgery with NCRT (n = 222) or who underwent R0 surgery alone (n = 347) were included. We performed uni- and multivariate analysis to identify prognostic factors for overall survival (OS) in patients with surgery after NCRT based on pTNM stages (AJCC 7^{th}).

Results: The 5-year OS rates for patients with ypTNM stage 0, 1 (including pT0N+M0), 2 and 3 in surgery after NCRT group were 74.1%, 51.6%, 29.4%, and 17.5% ($P < 0.001$), while those for patients with pTNM stage 0, 1, 2 and 3 in upfront surgery group were 92.9%, 81.3%, 61.7%, and 26.4%, respectively ($P < 0.001$). The 5-year survival rates of NCRT and upfront surgery groups in stage 1 and 2 showed distinct differences. In univariate analysis, age and clinical stage were associated with OS for ypTNM stage 0; clinical complete response (cCR) was for ypTNM stage 1; cCR, lymphovascular invasion (LVI), and perineural invasion (PNI) were for ypTNM stage 2; and LVI and PNI were for ypTNM stage 3, respectively. Subgroup analyses for each ypTNM stage are summarized in the Table.

Table: 631P Subgroup analysis of 5-year OS according to ypTNM stage

ypTNM Stage		5-year OS rate	p-value
0	Age <65, clinical stage 1–2	85.8%	0.005
	Age <65, clinical stage 3–4	76.9%	
	Age >65, clinical stage 1–2	71.5%	
	Age >65, clinical stage 3–4	44.7%	
1(including ypT0N+M0)	cCR	87.5%	0.008
	non-cCR	41.2%	
2	LVI (-), PNI (-), cCR	66.7%	0.089
	LVI (-), PNI (-), non-cCR	39.1%	
	LVI(+) and/or PNI (+)	0.0%	
3	LVI (-), PNI (-)	30.3%	0.029
	LVI (+) and/or PNI (+)	7.1%	

Conclusions: In patients with surgery after NCRT, pathologic prognostic factors (LVI and PNI) were significantly associated with the prognosis of advanced stages, whereas clinical prognostic factors (cCR, clinical stages and age) were of early stages. Although further studies are needed to validate the results of this study, we carefully suggest that clinical and pathological factors have a role in predicting survival outcome in detail based on ypTNM stage by stratifying each ypTNM stage into groups showing distinct survival profiles.

Legal entity responsible for the study: Asan Medical Center, Department of Oncology

Funding: None

Disclosure: All authors have declared no conflicts of interest.

632P Thromboembolic complications in patients with oesophagogastric adenocarcinoma undergoing preoperative chemotherapy

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Background: The scope of the present study was: to describe the incidence of thromboembolic events (TE) in patients (pts) with resectable oesophagogastric (OG) adenocarcinoma receiving preoperative chemotherapy (CT) with curative intent; to assess risk factors of developing TE; to determine their impact on patient outcome.

Methods: Data from 590 pts with OG adenocarcinoma, who received epirubicin, cisplatin and capecitabine (ECX) or 5-fluorouracil (ECF) preoperatively in 3 UK hospitals, between 2009 & 2016, were collected retrospectively.

Results: Median age was 66 years (range 28-85), 81% were males, 21% had gastric primaries, 98% received ECX chemotherapy, and 87% completed all 3 cycles of preoperative CT. In total, 52 pts (9%) had a venous and 22 (4%) an arterial event. Of patients with venous TE, 39 had pulmonary embolism and 13 deep vein thrombosis. Of patients with arterial TE, 7 developed cardiac infarct, 8 limb ischemia, 4 cerebrovascular accident and 3 superior mesenteric artery thrombosis. Arterial TE was associated with much higher inoperability rate compared to cases with venous TE or without TE (77% vs. 31% vs. 20% respectively, $p < 0.001$). Primary tumour location in the stomach (Odds ratio [OR] 3.24, 95%CI 1.72-6.12, $p < 0.001$), overweight (OR 3.11, 95%CI 1.33-7.26, $p = 0.009$) or obese status (OR 4.52, 95%CI 1.85-11.09, $p = 0.001$) and the presence of central venous access (OR 3.40, 95%CI 1.00-11.55, $p = 0.050$) were independent risk factors for venous TE development, while anticoagulant treatment was independently associated with a lower risk of venous TE (OR 0.22, 95%CI 0.06-0.83, $p = 0.026$). A very high Khorana score (of 4-5) was the only independent risk factor for arterial TE (OR 6.38, 95%CI 1.85-22.04, $p = 0.003$). Furthermore, arterial TE was an independent poor prognostic factor for OS when adjusted for baseline patient, tumour and treatment characteristics (Hazard ratio [HR] 3.02, 95%CI 1.85-4.95, $p < 0.001$).

Conclusions: Preoperative ECX/ECF chemotherapy for patients with resectable OG adenocarcinoma was associated with relatively high incidence of TE. However, only arterial TE affected patient outcome

Legal entity responsible for the study: Wasat Mansoor

Funding: None

Disclosure: All authors have declared no conflicts of interest.

633P Endoscopic resection for Barrett's esophagus: Uzbekistan experience

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Background: In the treatment of esophageal dysplasia, particularly Barrett's esophagus, radical endoscopic resection (SRER) has shown its effectiveness. The purpose of this study was to evaluate the long-term results of treatment of Barrett's esophagus dysplasia after a successful SRER.

Methods: Patients who received SRER for BE $\leq$ 5 cm with high-grade dysplasia (HGD) or early cancer (EC) achieved complete elimination of intestinal metaplasia (CE-IM) and neoplasia (CE-neo). Primary outcomes: relapse of neoplasia (HGD/EC), recurrence of dysplasia (including indefinite dysplasia) and recurrence of endoscopically visible BE. METHODS: Patients who received SRER for BE $\leq$ 5 cm with high-grade dysplasia (HGD) or early cancer (EC) achieved complete elimination of intestinal metaplasia (CE-IM) and neoplasia (CE-neo). Primary outcomes: relapse of neoplasia (HGD/EC), recurrence of dysplasia (including indefinite dysplasia) and recurrence of endoscopically visible BE.

Results: Hidden Barrett's glands, IM in biopsy specimens obtained distal to the normal emerging neo-squamocolumnar compound, the need for re-treatment, and sustained by CE-IM and CE-neo at the last follow-up endoscopy. RESULTS: 76 patients were included (65 men, mean age 66 years, median BE C2M3). The median follow-up was 76 months. A repetition of neoplasia was observed in 1 patient (T1bN0M0) after 130 months of observation and was treated with medical surgery (annual frequency 0.22% per year of the patient's observation). Four patients had recurrent dysplasia (0.87% per patient-year of follow-up). Twelve patients had recurrent endoscopically visible BE after median follow-up for 22 months (2.6% for each subsequent patient-year of observation), mostly small islands or languages. Five patients were found to have one Barrett burial gland finding (1.1% per year of the patient's observation), and 27 patients (5.9% per year of the patient's observation) showed MI in biopsies only distal to the neo-squamocolumnar junction was not reproduced in 56%. Repeated treatment was performed in 9 patients. CE-IM and CE-neo (excluding IM in the neon-squamolecular compound) in the last endoscopic endoscopy were seen in 95% and 97% of patients, respectively.

Conclusions: This study presents the longest published data on SRER to date. 6-year results show that a successful SRER is a long-term therapy for BE $\leq$ 5 cm with HGD/EC.

Legal entity responsible for the study: Tashkent Medical Academy

Funding: None

Disclosure: All authors have declared no conflicts of interest.

634P Risk of second malignancies after definitive therapy for esophageal cancer: A competing risk analysis

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Background: Esophageal cancer (EC) is associated with synchronous or metachronous cancer at other primary sites. However, few studies have evaluated second malignancies after treatment. We aimed to clarify the frequencies and risk factors of second malignancies after definitive therapy for EC.

Methods: EC patients (pts) who received definitive therapy at Aichi Cancer Center Hospital between 2000 and 2010 were retrospectively analyzed. Exclusion criteria were synchronous cancer or a past cancer history. We used competing risks regression model, which defined death and the development of second malignancies as competing risk, to conduct risk analyses. Standardized incidence rate (SIR) was calculated using population-based cancer registry.

Results: A total of 758 pts were included. Patient characteristics were as follows: male, 84%; median age, 64 (range, 32–84) years; squamous cell carcinoma, 94%; upper-third/middle-third/lower-third, 19/49/31%; clinical stage 0–I/II/III/IV, 28/24/45/3%; alcohol consumption history, 87%; smoking history, 86%. Chemotherapy, surgery, radiotherapy and endoscopic therapy were performed in 579 (76%), 374 (49%), 349 (46%), and 107 (14%) pts, respectively. With a median follow-up of 3.7 years, a total of 131 second malignancies were observed in 106 patients (14%). Cumulative incidences of second malignancies after 5 years were 7.6%. SIR of the patients was 1.83 [95% confidence interval (CI): 1.50–2.22]. Most common primary tumor sites were head and neck (20%), followed by lung (17%), stomach (16%), and colon and rectum (11%). Risk analyses revealed that age $\geq$ 65 [subdistribution hazard ratio (sHR): 1.51, 95% CI: 1.01–2.24, vs. <65] and clinical stage 0–I (sHR: 2.48, 95% CI: 1.46–4.22, vs. stage III and IV) and II (sHR: 2.10, 95% CI: 1.23–3.58, vs. stage III and IV) were associated with second malignancies. There was no significant association between second malignancies and treatment modalities.

Conclusions: EC pts are at a high risk of second malignancies after definitive treatment. Careful follow-up is required, especially in elderly pts or pts with early-stage.

Legal entity responsible for the study: Aichi Prefecture

Funding: None

Disclosure: All authors have declared no conflicts of interest.

635P Prognostic significance of local immunity factors in esophageal cancer

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Background: The purpose of the study was to assess possible prognostic significance of local immunity parameters in patients with esophageal cancer.

Methods: We studied tissues of tumor, peritumoral zone (PZ) and resection line (RL) obtained from 37 patients (11 women, 24 men aged 46–78 years) during surgical treatment of esophageal cancer with tumors located in the upper (1), mid (16), lower (19) thoracic esophagus and its abdominal part (1 patient). Histological study showed squamous cell carcinoma, keratinizing in 27 and non-keratinizing in 10 patients. Differentiation of tumors was G3, G2 and G1 in 7, 19 and 11 patients, respectively. The follow-up period lasted from 11 to 22 months. 10 patients received postoperative multi-course CF polychemotherapy. Metastases to distant lymph nodes developed in 13 patients, metastases to parenchymal organs in 6 patients; 7 patients died. 16 patients did not show signs of progression during the follow-up period. Subsets of T, B and NK-lymphocytes were determined in homogenates of tissues obtained during surgery using the FACSCantoII flow cytometer (BD) with a panel of antibodies CD45, CD3, CD4, CD8, CD19, CD16/56; levels of T-regs (CD4+CD25+CD127dim) were also assessed. Percentages of lymphocytes were calculated from the total lymphocyte number, T-regs – from the number of CD3+CD4+ cells.

Results: The ratios of percentages of different lymphocyte subsets were compared in presence or absence of the disease progression during a follow-up period. The ratio of T-regs in PZ to the level in tumor in patients with further progression was 0.643 ± 0.3, while in patients without progression it was significantly lower -0.15 ± 0.033 ($p < 0.05$). The ratio of T-regs in PZ to the level in RL during a follow-up period in patients with progression was -2.8 ± 0.43, without progression -0.57 ± 0.126 ($p < 0.05$). On the contrary, the coefficient of CD3+CD8+ cells in RL to their level in tumor was lower in patients with progression (0.91 ± 0.153) than in patients without it (1.33 ± 0.32) ($p < 0.05$).

Conclusions: The ratios characterizing local immunity (PZ/tumor and PZ/RL for T-regs and RL/tumor for CD3+CD8+ lymphocytes) in patients with esophageal cancer proved to have prognostic significance for progression.

Legal entity responsible for the study: Rostov Research Institute of Oncology

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Disclosure: All authors have declared no conflicts of interest.

636P Recent advance in enhanced recovery after esophagectomy: A systematic review and meta-analysis

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Background: Many studies have shown that enhanced rehabilitation after surgery (ERAS) protocol can be closely linked to the reduced hospital stay and better outcomes of cancer patients, including those with esophageal carcinoma. However, not all studies have generated encouraging results. Therefore, a systematic review and meta-analysis of recent advance evidence to evaluate the significance of ERAS following esophagectomy was conducted.

Methods: A literature search was performed in Medline, Embase, Pubmed, CINAHL, and the Cochrane library for articles describing an enhanced rehabilitation after surgery protocol in esophagectomy for esophageal cancer published between January 2010 and December 2016. The primary outcome measure was postoperative cardiac or pulmonary complication rates. Secondary outcome measures were postoperative length of stay, readmissions, and mortality. Statistical analysis was carried out using Comprehensive Meta Analysis 2.0.

Results: The literature search identified 118 potentially relevant papers. 12 papers met the inclusion criteria for the review: 7 case-control studies, 3 retrospective studies, and 2 prospective randomized controlled study, describing a total of 1,895 patients. Meta-analysis of six studies focusing on pulmonary complications showed that there was a significant difference in favor of the ERAS group (OR = 0.625, 95% confidence interval (CI) 0.479–0.815, p = 0.001; I^2=0%). Implementation of an ERAS protocol led to a significant decrease in cardiac complications (OR = 0.656, 95% confidence interval (CI) 0.474–0.907, p = 0.011; I^2=12.905%). Postoperative length of hospital stay was significantly shorter in ERAS group [standard mean difference = −2.058d, 95%confidence interval (CI) −3.202 to − 0.913, P = 0.000; P for heterogeneity =0.000, I^2=96.109%]. Introduction of an ERAS protocol did not result in an increase in anastomotic leak, chyle leak, mortality or readmissions. There was no significant difference in ICU stay and hospital cost.

Conclusions: ERAS protocol as compared with conventional procesure may reduce postoperative hospital stay and cardiac or pulmonary complication rates in patients undergoing esophagectomy for esophageal cancer.

Legal entity responsible for the study: 4th Hospital Hebei Medical University

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Disclosure: All authors have declared no conflicts of interest.

637P High thromboembolic event rate in patients with locally advanced esophageal cancer during perioperative therapy: A pre-planned analysis of the intergroup phase III trial SAKK 75/08

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Background: High rates of venous thromboembolic events (VTE) are reported for patients (pts) with upper GI-cancers (stomach, pancreas) and treatment with Cisplatin (Cis), but mainly in retrospective analyses and in advanced disease. A prospective analysis of VTE in pts with resectable esophageal cancer is warranted.

Methods: Pre-planned analysis of VTE in a multicenter phase III trial according to reported AEs and SAEs from start of preoperative treatment until 6 months postoperatively. Pts with resectable esophageal cancer (T2N1-3; T3-4aNx) received 2 cycles of induction chemotherapy (CT) with Docetaxel (Doc) 75mg/m^2, Cis 75 mg/m^2 followed by chemoradiation (CRT) with 45 Gy, Doc 20 mg/m^2 and Cis 25 mg/m^2 weekly and then surgery or were randomly assigned to the same treatment with addition of neoadjuvant and adjuvant cetuximab.

Results: Of 300 pts 29 VTE were reported in 26 pts with an incidence rate (IR) of 8.7%. 3 pts had 2 VTE. 72% (21/29) of all VTE occurred preoperatively. No significant difference between treatment arms was found, odds ratio (OR) 0.8 [95%CI 0.4-1.9], p = 0.7. Grades (G) of VTE according to CTCAE v4.0: 3% (1/29) G1, 41% (12/29) G2, 45% (13/29) G3 and 10% (3/29) G5. In a multivariable logistic regression including baseline hemoglobin, platelets, neutrophils, BMI, treatment arm and histology, only adenocarcinoma (IR 11.1%, 21/189) compared to squamous cell cancer (IR 4.5%, 5/111) was significantly associated with VTE-risk during treatment, OR 2.9 [95%CI 1.02;8.4], p = 0.046. Baseline Khorana risk score (KRS) for VTE was 0 in 73% (19/26), 1-2 in 23% (6/26) of pts and 3 in one patient with VTE ($\geq$ 3 equal to high-risk and recommendation for prophylaxis). Median PFS in pts with VTE was 2.1 yrs vs. 2.5 yrs for pts without VTE.

Conclusions: This first prospective analysis of VTE in resectable esophageal cancer pts reveals a high IR during perioperative therapy of almost 9% comparable to high-risk pts according to KRS. Only one of these pts would have been identified by KRS as high-risk. Prophylactic anticoagulation balanced against individual bleeding risks could be considered in esophageal cancer pts treated with neoadjuvant Cis-based CT and RCT, especially in adenocarcinoma.

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Legal entity responsible for the study: Swiss Group for clinical Cancer research (SAKK)

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Disclosure: P. Thuss-Patience: Advisory boards: Roche, BMS, Nordic, MSD, Pfizer, Lilly. Research funding: Novartis. M. Bitzer: Consulting/advisory boards: Bayer Healthcare, BMS. W. Eisterer: Advisory boards: Roche, Merck, Amgen, Lilly, Celgene. M. Stahl: Advisory board: MSD, Amgen, Sanofi, Servier. T. Ruhstaller: Advisory boards: Novartis, Roche, Astra-Zeneca. All other authors have declared no conflicts of interest.

638P Two year survival and safety update for esophageal squamous cell carcinoma treated with nivolumab (ATTRACTION-01/ONO-4538-07)

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Background: Nivolumab (Nivo) monotherapy has demonstrated clinical activity and safety for esophageal cancer refractory or intolerant to standard chemotherapy (Lancet oncology, online March 14, 2017, http://doi.org/10.1016/S1470-2045(17)30181-X). We report updated results base on a minimum follow-up of 2-years.

Methods: Patients aged ≥ 20 years with ECOG PS 0-1 were enrolled and treated with Nivo (3 mg/kg, IV, Q2W) until progression or unacceptable toxicity. The primary endpoint was objective response rate (ORR) evaluated by independent review committee according to RECIST 1.1. Other endpoints included safety, overall survival (OS), progression-free survival (PFS) and duration of response (DOR).

Results: Between February 25, 2014 and November 14, 2014, 65 patients with esophageal squamous-cell carcinoma were enrolled; median age of 62 years (range 49-80); male/female, 54/11; ECOG PS 0/1, 29/36; median number of 3.0 (range 1-8) prior regimens. The primary endpoint of ORR was 17.2% (11/64 patients, CR/PR: 1/10, 95% confidence interval [CI] 9.9, 28.2) as of May 17, 2015. Median OS and PFS were 10.8 and 1.5 months. With a minimum follow-up of 2-years (cutoff date November 17, 2016), 6 patients remained on treatment with Nivo. The ORR was 17.2% (CR/PR: 3/8) and median DOR was 11.17 months (95% CI 3.02, -). The Kaplan-Meier estimated 1-, 1.5- and 2-years OS rate were 45.3% (95% CI 32.9, 56.9), 25.0% (15.2, 36.0) and 17.2% (9.2, 27.3). One, 1.5- and 2-years PFS rate were 10.3% (95% CI: 4.2, 19.4), 8.6% (3.2, 17.3) and 8.6% (3.2, 17.3). Adverse events (AEs) were reported in 56 (86.2%) of 65 patients including grade 3 − 4 AEs reported in 19 patients (29.2%). The most common AEs were diarrhea (21.5%), decreased appetite (18.5%), lung infection (13.8%) and cough (12.3%). Seven patients (10.8%) discontinued the study treatment due to drug-related AEs, while no treatment-related death was reported.

Conclusions: Nivo suggest a durable, long-term survival benefit with 17.2% of patients alive at 2-years. These data support ongoing phase III study (NCT 02569242) assessing Nivo monotherapy compared with docetaxel or paclitaxel.

Clinical trial identification: JapicCTI-No.142422

Legal entity responsible for the study: Ono Pharmaceutical Co., Ltd

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639P A phase II study of TAS-102 for advanced/recurrent esophageal cancer refractory/intolerable to standard therapies

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Background: There is no effective chemotherapy for patients with esophageal squamous cell carcinoma (ESCC) refractory or intolerant to 5-FU, platinum, and taxanes. TAS-102 is an oral combination drug of trifluridine and tipiracil hydrochloride. Our preclinical study showed that TAS-102 has antitumor activity against 5-FU resistant esophageal cancer cells. We conducted this study to evaluate the safety and efficacy of TAS-102 in ESCC patients who were refractory or intolerant to standard treatment (UMIN000019268).

Methods: Patients with histologically proven advanced or recurrent ESCC, which had been refractory or intolerable to 5-FU, platinum, and taxanes, were eligible. Patients also had to satisfy following criteria: >20 years of age; ECOG performance status 0 or 1; adequate organ functions. TAS-102, 35 mg/m2 bid, was administered on days 1-5 and 8-12 for the first 2 weeks followed by 2-week rest. The regimen was repeated every 4 weeks until disease progression, serious adverse event, or refusal. Primary endpoint was progression-free survival rate at 3 months (PFS3). With expected PFS3 of 25% to 30% and the null hypothesis of 10% under 80% power and a one-sided significance level of 5%, 35 patients was needed.

Results: A total of 42 patients were enrolled. 90% of the patients were male, 95% had distant metastasis, and 98% had target lesion (s). As of data cutoff, 34 events were observed. PFS3 was 15.4% (90% CI: 7.4%, 26.0%), which did not reject the null hypothesis. Median PFS and OS were 1.3 months and 4.5 months, respectively. Response rate was 0%, although 24% (10/42) of patients achieved stable disease. There were 3 patients not evaluable for response. Major treatment related adverse events of grade ≧3 were: neutrophil count decreased (48%), febrile neutropenia (7%), and appetite decreased (5%). No treatment related death was observed.

Conclusions: TAS-102 was feasible and showed modest efficacy in patients with refractory ESCC.

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Legal entity responsible for the study: Kyoto University Hospital

Funding: Taiho Pharmaceutical Co. Ltd.

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640P Dual CDK 4/6 inhibitor demonstrates potent antitumor efficacy in vitro and in vivo against esophageal adenocarcinoma

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Background: Esophageal adenocarcinoma (EAC) is a leading cause of cancer deaths, and current treatment options are limited. Cell cycle regulators CDK4 and CDK6 are progressively upregulated in EAC carcinogenesis and associated with poor prognosis. The modified Levrat model of esophagojejunostomy (EJ) in a rat has demonstrated well-documented utility for *in vivo* efficacy testing against *de novo* EAC. In the present study, we evaluate a dual CDK4/6 inhibitor, abemaciclib, for the treatment of EAC.

Methods: Human EAC cell lines, OE33 and FLO1, were used to evaluated proliferation and apoptosis using BrdU and flow cytometry, respectively. EJ was performed on 38 Sprague-Dawley rats to induce gastroduodenoesophageal reflux and the subsequent development of EAC. At 36 weeks post-operatively, rats were randomized to receive IP abemaciclib at 26 mg/kg per day or placebo (acetate buffer) for 4 weeks. Drug efficacy was evaluated with MRI, endoscopic biopsy, gross histological evaluation, and CDK4/6 pathway expression by RT-PCR.

Results: With an established ED50 of 6μM in OE33 and 14μM in FLO1, proliferation decreased with treatment by 89.5% and 87.5%, respectively. Flow cytometry

demonstrated an increase of apoptosis by 45.6% and 38.9%, respectively. Twenty of 23 (87.0%) treated animals and all of 18 (100%) control animals reached study endpoint. Treatment group mortality consisted of rats afflicted with moderate peritonitis, diarrhea, and weight loss. Mean MRI tumor volume decreased by 151.0% in treatment animals and increased by 108.3% in control animals ($p < 0.01$). Treatment with abemaciclib demonstrated tumor volume increase in 0% (control = 66.7%) ($p < 0.01$), decrease in 79% (control = 0%) ($p < 0.01$), and stable volume in 21.1% (control = 33.3%) ($p = 0.41$). EAC prevalence in treatment animals decreased by 48.2%; whereas, prevalence in control animals increased by 5.5% ($p < 0.01$). mRNA expression, pre- and post-treatment, demonstrated significant downregulation of CDK4, CDK6, RB1, pRB1 and Cyclin-D ($p < 0.05$).

Conclusions: Abemaciclib exhibits potent in vitro and in vivo antitumor efficacy in EAC models, providing the rationale for future clinical testing.

Legal entity responsible for the study: Eli Lilly and Co.

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641P The influence of body composition on the systemic exposure of paclitaxel in esophageal cancer patients

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Background: Weight loss and malnutrition are common symptoms of esophageal cancer, which can lead to skeletal muscle wasting and loss of adipose tissue. It was hypothesized before that the pharmacokinetics (PK) of chemotherapy may depend on body composition (Prado et al, 2013). In addition, we earlier showed that the clearance (CL; L/h) of unbound paclitaxel (pac) is related to body-surface area (BSA; m^2) and gender (Bins et al, 2014). Therefore, now we aimed to assess the relationship between pac CL and body composition.

Methods: We analyzed 197 patients with stage III esophageal cancer who were treated with pac and carboplatin in a prospective study between 2008 and 2013. CL of pac, which was estimated using nonlinear mixed effects modeling (NONMEM) was used as a measure of systemic pac exposure (de Graan et al, 2012). Skeletal muscle index (SMI, cm^2/m^2), muscle attenuation (MA) and visceral adipose tissue (VAT; cm^2) were measured at the level of the 3rd lumbar vertebra on computed tomography (CT) scans performed before treatment. Gender-specific differences in pac CL, based on the 1st quartile and the 4th quartile of the SMI and VAT measurement were analyzed with a Mann-Whitney test. A Spearman rank correlation (r) was calculated to explore the relationship between pac CL and SMI, VAT and MA, respectively.

Results: CT images and pac PK data were available for 183 patients (78% was men). Pac CL was correlated with SMI ($r = .27$, $p = .001$) and VAT ($r = .28$, $p = .001$), while no correlation was found with MA ($r < .01$, $p = .91$). Interestingly, while in male patients with the highest SMI a higher pac CL was found compared to the lowest SMI ($p = .024$), and also for the 1st and 4th quartile of VAT ($p = .003$), in female patients no effect of SMI and VAT on pac CL was seen.

Conclusions: Skeletal muscle mass and visceral adipose tissue are positively correlated with pac CL in male patients with esophageal cancer. Differences in body composition between men and women may potentially explain the difference in the outcome of this analysis, and may also partly explain the difference in pac CL between both genders. Although the effect sizes are too small to support dose adaptions based on VAT or SMI, these parameters partly explain the large interpatient variability in pac PK.

Legal entity responsible for the study: Erasmus MC Cancer Institute

Funding: None

Disclosure: All authors have declared no conflicts of interest.

642P Survival in advanced oesophagogastric adenocarcinoma (OGA) improves with the use of multiple lines of therapy: Results from an analysis of over 500 patients (pts)

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Background: Palliative chemotherapy (CT) remains the primary mode of treatment for advanced OGA and is shown to improve survival in the 1st and 2nd line setting. We sought to evaluate the use of systemic therapy and assess survival outcomes for pts with advanced OGA treated at the Royal Marsden Hospital (RMH).

Methods: Retrospective analysis of consecutively treated pts receiving at least 1 cycle of CT for advanced OGA at RMH between April 2009 - Nov 2015.

Results: 511 pts were identified; 75% male, 25% female; median age at diagnosis 66 yrs (range 24-90). Treatment intent at initial diagnosis was radical in 21% (with subsequent relapse) and palliative in 79%. There was no significant difference in median overall survival (OS) in the advanced setting between pts with relapsed disease after initial radical treatment and pts with metastatic disease at diagnosis (12.6 vs 11.3m; $p = 0.10$). OS was significantly improved for confirmed HER2+ve pts compared to HER2-ve (15.0 vs 11.9m; $p = 0.02$). OS was significantly improved in pts treated within a therapeutic clinical trial at any line of treatment compared with those who were not (13.5 vs 10.1m; $p = 0.02$). Survival was significantly correlated with number of treatment lines received ($p < 0.001$).

Conclusions: We have demonstrated the pattern of usage of systemic therapy for over 500 patients treated within a single UK oncology centre. Survival outcome remains poor for the majority of pts who have 1st line CT only. Pts suitable for sequential CT have better outcomes and entry into clinical trials is associated with improved survival. There remains a need to define evidence-based therapies for the small but increasing proportion of pts suitable for treatment in the 3rd line and beyond.

Legal entity responsible for the study: Dr N Starling, Royal Marsden Hospital NHS Foundation Trust, Gastrointestinal medical oncology unit.

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643P The research progress in randomized, multicenter, controlled evaluation of S-1 and oxaliplatin as neoadjuvant chemotherapy for advanced gastric cancer patients

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Background: There is differrence beteween the perioperative and adjuvant chemotherapy in east and west country, but there is no study to compare the effect between the perioperative and adjuvant chemotherapy based on the D2 gastrectomy in advanced gastric cancer till now. Our study wants to evaluate the efficacy and safety of S-1 and oxaliplatin as neoadjuvant chemotherapy for advanced gastric cancer.

Table: 642P

	1st line	2nd line	3rd line	>3 lines
N	511 (100%)	200 (39%)	70 (14%)	15 (3%)
Treatments	Triplet 63% Doublet 33% Single 4%	Triplet 12% Doublet 34% Single 54%	Triplet 3% Doublet 37% Single 60%	
Clinical trial	103 (20%)	57 (29%)	25 (36%)	5 (33%)
Median no. cycles	6	3	3	
ORR	CR 2% PR 47% SD 29%	CR 0% PR 20%, SD 34%	CR 0% PR 19% SD 24%	
PFS (m)	5.5	3.0	1.8	
OS (m)	11.5 (whole cohort)			
OS (m)	8.3 (1st line only received)	14.0 (1st + 2nd line received)	20.1 (1st, 2nd + 3rd line received)	33.0 (>3 lines received)

Methods: Between September 2012 and December 2016, 420 patients with clinical stage IIA-IIIC gastric cancer were eligible for inclusion. They were randomly assigned to either the neoadjuvant chemotherapy group (n = 210) or the adjuvant chemotherapy group (n = 210). The reaction rate, effective rate, T-stage, incidences of adverse reaction, surgical R0 resection rate, CY1 rate and pCR rate in the two groups were compared.

Results: In neoadjuvant chemotherapy group, the reaction rate, effective rate, and pCR rate were 80%, 40% and 20% respectively. The surgical R0 resection rate (80% vs 70%) were much higher in neoadjuvant chemotherapy group. There was no significant difference in incidences of adverse reaction between the two groups. However, the CY1 rate (5% vs 8%) was lower and T-stage was earlier in neoadjuvant chemotherapy group.

Conclusions: S-1 and oxaliplatin as neoadjuvant chemotherapy is effective for advanced gastric cancer, and there was no increase of adverse reaction.

Clinical trial identification: NCT01583361, April 4, 2012

Legal entity responsible for the study: Lin Chen

Funding: National Natural Science Foundation of China and Beijing Nova program

Disclosure: All authors have declared no conflicts of interest.

644P The N stages for early gastric cancer should differ from those of advanced gastric cancer: Results based on the SEER database

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Background: The aim of this study was to establish an appropriate N staging system for early gastric cancer (EGC).

Methods: Data from 24,223 patients who underwent radical gastrectomy between 1988 and 2011 were retrieved from the National Cancer Institute's Surveillance, Epidemiology, and End Result (SEER) database. The optimal cutoff value for the number of LNs was determined by the X-tile program. The overall survival (OS) based on eighth edition and new TNM staging systems were compared, and the analysis was repeated in an external validation set.

Results: In the same T category, the OS rates were significantly different in each N category for advanced gastric cancer (AGC). However, no significant differences were observed in OS between N1 and N2 cancers or between N3a and N3b cancers in cases of EGC. The X-tile program identified that the difference in survival was most significant when 6 metastatic LNs were present. The new staging system for EGC consisted of T1N0, T1N1' (1-6 metastatic LNs) and T1N2' (≥7 metastatic LNs). Compared with the eighth edition of the TNM staging system, the OS of patients in the T1N1' stage was similar to that of patients with stage IIA disease, whereas the OS of patients in the T1N2' stages was similar to that of patients with stage IIB disease ($P < 0.05$). The new TNM staging system exhibited slightly superior prognostic stratification with lower AIC values and higher $\chi 2$ and c-statistic compared with the eighth edition of the TNM classification system. Similar results were found in the external validation dataset from the Fujian Medical University Union Hospital (FMUUH) database.

Conclusions: The N category of the eighth edition of the AJCC TNM classification exhibits variation in the survival of patients with AGC. However, this classification remains associated with some stage migration in EGC and the proposed N category permits better prognostic prediction.

Legal entity responsible for the study: Changming Huang

Funding: None

Disclosure: All authors have declared no conflicts of interest.

645P Young-onset gastric cancer: The role of microbial factors

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Background: Gastric cancer (GC) is a leading cause of cancer death, associated with environmental and genetic factors, with increasing incidence in young patients. Recently, as part of the Cancer Genome Atlas (TCGA) project, a comprehensive molecular characterization of gastric adenocarcinoma revealed unique molecular and genetic patterns that were classified GC into four subtypes among which is the Epstein-Barr Virus (EBV)-associated subtype. The EBV-associated subtype is positive for the virus, displays unique genomic landscape and represents 8.7% of the cohort of the TCGA. Since most of the young-onset GC is sporadic and non-hereditary upon former studies, environmental factors may play a role in the pathogenesis of GC among young patients. We hypothesized that the prevalence of EBV-subtype may be higher in young-onset GC than in the average-onset.

Methods: Tissue tumor samples of matched cohorts of young-onset (<45y) and average-onset (>60y) were retrospectively retrieved, DNA was extracted and analyzed by quantitative PCR (qPCR) for EBV using two different EBNA primers to validate the detection of the virus. Clinical data among which patient demographics, tumor location and family history were extracted from medical records and correlated to age.

Results: Twenty-nine young-onset GC patients and 34 average-onset GC patients were enrolled into the study. Median age for the young-onset was 34y (range 21-45) and for the average-onset 69y (60-90). Thirty-six percent of the young-onset were male, compared with 57% in the average-onset. Family history was more prevalent in the average-onset cohort (37% vs. 29%). The distribution of the tumor location differed between the two groups – whereas in the young-onset 36% of the tumors were in the body of the stomach compared with 46% of the average-onset that were in the antrum. EBV was significantly more prevalent in the young-onset cohort (32.1% compared with 11.4% in the average-onset).

Conclusions: Our study indicate that EBV may play a key role in the pathogenesis of young-onset GC. Since young-onset GC is not predominated by hereditary factors, environmental and microbial factors should be further studied as essential contributors, what may potentially govern early detection in high risk populations.

Legal entity responsible for the study: Irit Ben-Aharon

Funding: None

Disclosure: All authors have declared no conflicts of interest.

646P Comprehensive complication index (CCI) predicts cancer-specific survival of patients with postoperative complications after curative resection of gastric cancer

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Background: To investigate prognostic impact of postoperative complications for patients with gastric cancer.

Methods: Postoperative complications of patients undergoing radical gastrectomy for gastric cancer were reviewed. The severity of complications was graded by the CCI and C-D classification.

Results: A total of 5327 patients were included in the study. Complications were observed in 767 patients. When the C-D classification system was applied, for patients with grade I-II complications, the length of stay (LOS) of those with high CCI (CCI ≥ 26.2) was significantly longer than that of patients with low CCI (CCI<26.2) ($p < 0.001$). The 5-year cancer-specific survival rate of the patients with complications (52%) was lower than that of patients without complications (61%) ($p < 0.001$). Analysis of the factors associated with prognosis in patients with gastric cancer revealed that complications were independent risk factors for specific survival. When CCI was used to classify complication severity, the 5-year cancer-specific survival rate of the high CCI group was 46.3%, which was lower than that of the low CCI group (54.9%, $p = 0.009$).

Conclusions: Complication after radical gastrectomy is an independent prognostic factor, and the complication severity as graded by CCI reflects the difference of cancer-specific survival in gastric cancer patients with postoperative complications.

Legal entity responsible for the study: Changming Huang

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Disclosure: All authors have declared no conflicts of interest.

647P ATM loss, MSI and survival in the MAGIC trial

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Background: Loss of ataxia-telangiectasia mutated (ATM) protein has been associated with worse prognosis in resected gastric cancer (GC), and may predict sensitivity to drugs targeting DNA damage pathways. Microsatellite instability (MSI) is prognostic in surgically treated GC patients (pts) and may be negatively prognostic in perioperative chemotherapy (chemo) treated GC. We examined the effect of ATM and MSI on overall survival (OS) for pts randomised to surgery alone or perioperative ECF chemo in the MRC MAGIC trial.

Methods: ATM was assessed using anti-ATM antibody (clone Y170) on 4 μm TMA sections. ATM negative (neg) tumours had >90% cells neg for nuclear ATM. MSI was assessed using Promega MSI System. MSS tumours had all markers stable; MSI-L had only 1 unstable marker; MSI-H had at least 2 unstable markers. Trial arms were analysed independently.

Results: 39 of 225 evaluated pts (17%) were ATM-neg. Pts with/without ATM data had similar OS. Clinicopathological characteristics were similar between ATM-neg and positive (pos) pts. 217 pts had MSI and ATM status available: MSI and ATM status were highly correlated (ATM-neg/MSS n = 27, ATM neg/MSI-H n = 10, ATM-pos/MSS n = 175, ATM-pos/MSI-H n = 5, $p < 0.001$). Median OS for all biomarker groups is detailed in the table.

Table: 647P Overall survival (OS) by ATM, MSI and treatment arm

	subjects	Events	Median OS	95% CI for Median OS		HR	95% CI for HR		Cox PH test
Surgery alone arm: OS from surgery by ATM status									
ATM neg	22	10	48.3	8.5	NE	1.3	0.7	2.6	0.41
ATM pos	105	74	23.4	18.9	31.2				
Surgery alone arm: OS from surgery, by ATM and MSI status									
ATM neg MSS	14	10	15.4	3.4	48.3				
ATM pos MSS	102	73	23.4	18.9	31.2	0.80	0.4	1.6	0.51
ATM neg MSI-H	5	0	NE	NE	NE				
ATM pos/MSI-H									
Chemotherapy + surgery arm: OS from surgery by ATM status									
ATM neg	17	8	na	5.8	na	1.5	0.7	3.1	0.32
ATM pos	81	55	19.6	13.4	35.2				
Chemotherapy+ surgery arm: OS from surgery by ATM and MSI status									
ATM neg MSS	11	5	NE	NE	NE				
ATM pos MSS	73	50	19.6	13.4	35.2	1.7	0.7	4.3	0.24
ATM neg MSI-H	4	3	5.8	NE	NE				
ATM pos MSI-H	5	4	9.7	NE	NE	0.8	0.8	3.8	0.78

Conclusions: In MAGIC, ATM status was not prognostic for OS in either treatment arm. ATM loss was much more common in MSI-H pts. In this relatively underpowered analysis, chemo treated MSS-ATM-neg pts had encouraging OS. In chemo treated pts, prognosis was poor for MSI-H patients independent of ATM status. Further evaluation of ATM, MSI and chemo outcomes may be justified.

Legal entity responsible for the study: Medical Research Council

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648P Negative lymph node count is a significant prognostic factor in patient with stage IV gastric cancer after palliative gastrectomy

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Background: Negative lymph node (NLN) count has been validated as a protective predictor in various cancers after radical resection. However, the prognostic value of NLN count in the setting of gastric cancer patients who have received palliative resection has not been investigated. The aim of the present study was to explore the effect of NLN counts on the survival outcomes in patients with stage IV gastric cancer after palliative resection.

Methods: Surveillance, Epidemiology, and End Results Program (SEER)-registered gastric cancer patients were used for analysis in this study. Kaplan-Meier survival curves and multivariate Cox proportional hazards model were used to assess the risk factors for survival.

Results: A total of 1,495 patients with stage IV gastric cancer underwent palliative resection were identified from SEER database between 2004 and 2011. It showed that NLN count ($P < 0.001$) and N stage ($P < 0.001$) were independently prognostic factors in patients with stage IV gastric cancer after palliative surgery. X-tile plots identified 2 and 11 as the optimal cutoff values to divide the patients into high, middle and low risk subsets in term of cause-specific survival (CSS). And NLN count was proved to be an independently prognostic factor in multivariate Cox analysis (2-10, HR = 0.762, 95% CI: 0.660-0.880, ≥11, HR = 0.525, 95% CI: 0.437- 0.632, $P<0.001$, 0-1 as reference). The risk score of NLN counts demonstrated that the plot of hazard ratios (HRs) for NLN counts sharply increased when the number of NLN counts decreased.

Conclusions: Our present study revealed that NLN count was an independent prognostic predictor in stage IV gastric cancer after palliative resection. Standard lymph node dissection, such as D2 lymphadectomy maybe still necessary during palliative resection for patients with metastatic gastric cancer.

Legal entity responsible for the study: N/A

Funding: None

Disclosure: All authors have declared no conflicts of interest.

649P PD-L1 expression in primary tumours and paired lymph node metastases in chemoradiotherapy-naïve esophageal and gastric adenocarcinoma: Relationship with MSI status and prognosis

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Background: Although neoadjuvant and/or adjuvant treatment enhances survival in patients with resectable esophageal and gastric (EG) cancer, the prognosis remains poor and there is a great need to identify novel treatment strategies and suitable biomarkers. The efficacy of immune-modulating therapies in EG cancer remains to be confirmed. Expression of programmed death ligand 1 (PD-L1) is, together with microsatellite instability (MSI) status, a putative biomarker of response to such therapies, but their prognostic value in EG cancer remains unclear. Therefore, the aim of this study was to examine the expression of PD-L1 in tumour cells (TC) and tumour-infiltrating immune cells (IC) in chemoradiotherapy-naïve primary EG tumours and paired lymph node metastases. Particular attention was given to the relationship with MSI status and prognosis.

Methods: PD-L1 expression in TC and IC was assessed by immunohistochemistry (IHC) on tissue microarrays with all primary tumours (n = 165) and paired lymph node metastases (n = 61) from a retrospective consecutive cohort of patients with chemoradiotherapy-naïve resected EG cancers. MSI was defined as loss of IHC expression of MLH1, MSH2, MSH2 or MSH6. Univariable and multivariable Cox regression analysis was used to calculate overall survival (OS).

Results: There was a significant correlation between TC and IC PD-L1 expression in primary tumours ($p < 0.001$) but not in metastases. There was no significant association between TC PD-L1 expression in primary tumours and metastases, but IC PD-L1 expression was significantly higher in metastases ($p = 0.027$).There were strong significant associations between PD-L1 expression in TC and IC, respectively, and MSI ($p < 0.001$ for both). Neither TC PD-L1 expression nor MSI status was prognostic. However, high IC PD-L1 expression (>50%) was significantly associated with a prolonged OS, independent of conventional prognostic factors and MSI status (HR = 0.39, 95% CI 0.15-0.99).

Conclusions: PD-L1 expression in TC does not differ significantly between primary tumours and lymph node metastases, PD-L1 expression in IC but not in TC is an independent favourable prognostic factor.

Legal entity responsible for the study: Lund University

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Disclosure: All authors have declared no conflicts of interest.

650P Effects of preoperative malnutrition on short- and long-term outcomes of patients with gastric cancer: Can we do better?

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Background: This study aimed to examine the effect of preoperative nutritional status on short- and long-term outcomes in patients who underwent radical gastrectomy. It also explored the role of preoperative correction of hypoalbuminemia (PCH) in malnourished patients with gastric cancer.

Methods: We prospectively reviewed data from patients with gastric cancer who were treated in our department between January 2009 and December 2014. The effect of preoperative nutritional status on short- and long-term outcomes in patients who underwent radical gastrectomy was investigated. We explored whether PCH could improve the short- and long-term outcomes of these patients.

Results: A total of 1,976 patients were analyzed, including 412 in the malnourished group and 1,564 in the well-nourished group. The overall incidence of complications in the malnourished group was significantly higher than that of the well-nourished group (21.4% vs 15.5%, $p = 0.005$). Except for incision infection (3.2% vs 1.6%, $p = 0.041$), there were no significant differences for other complications. In the malnourished group, 98 cases of preoperative hypoproteinemia were corrected (PCH group), whereas 314 cases were not (NPCH group). The incidence of incision infection in the PCH group was significantly lower than that in the NPCH group (0% vs 4.1%, $p = 0.041$). The median follow-up time was 39 months (1.0–88.0 months). The 3-year overall survival (OS; 59.1% vs 75%, $p < 0.001$) and disease free survival (DFS; 54.8% vs 72.5%, $p < 0.001$) were significantly lower in the malnourished group than in the well-nourished group. A multivariate Cox regression analysis showed that malnutrition was an independent prognostic factor for 3-year OS (HR = 1.255 (1.008-1.490), $p = 0.041$) and DFS (HR = 1.179 (1.012-1.411), $p = 0.046$). For the malnourished group with stage I gastric cancer, the PCH group and the NPCH group showed no significant differences in 3-year OS (90.0% vs 89.0%, $p = 0.227$) or DFS (90.0% vs 87.3%, $p = 0.363$). However, for the malnourished group with stage II/III gastric cancer, the 3-year OS (69.9% vs 47.6%, $p = 0.013$) and DFS (55.4% vs 43.6%, $p = 0.046$) were significantly higher in the PCH group than in the NPCH group.

Conclusions: The incidence of incision infection was significantly higher in patients with malnutrition than in well-nourished patients. The 3-year OS and RFS were significantly lower in malnourished patients than in well-nourished patients. PCH can both reduce the incidence of incisional infection in patients with malnutrition and significantly improve the 3-year OS and RFS for malnourished patients with stage II/III gastric cancer.

Legal entity responsible for the study: Changming Huang

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Disclosure: All authors have declared no conflicts of interest.

651P Is there any relationship between Helicobacter pylori infection and HER2 expression in gastric cancer?

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Background: Helicobacter pylori (HP) is a significant causative agent of gastric cancer (GC). However, the underlying mechanisms involved in its pathogenesis and association with oncoproteins are unclear. The aim of the present study was to evaluate the relationship between HP infection and human epidermal growth factor receptor 2 (HER2) expression in gastric cancer patients.

Methods: Surgery (173) or endoscopic biopsy (35) specimen of 208 patients diagnosed with GC was evaluated for the presence of HER2 and HP. HER2 expression was assessed by fluorescence in situ hybridization (FISH) method, whereas HP status was evaluated histologically. Giemsa stain was used to identify HP status, in case HP could not be recognised in routine hematoxylin eosin stained sections despite careful examination.

Results: The median age was 63 years (27-91) and most patients were male (male/female: 149/59). Histopathologic diagnosis was adenocarcinoma in 117 (56.2%), signet ring cell adenocarcinoma in 51 (24.6%), and mixed adenocarcinoma-signet ring cell adenocarcinoma in 40 patients (19.2%). Of all 208 patients, HP was positive in 87 (41.8%) and negative in 121 (58.2%) patients. FISH positivity for HER2 was observed in 41 (19.7%), whereas FISH negativity was observed in 167 (80.3%) patients. According to the Chi-square test, patient distribution were 21 in HER2 positive HP negative group, 20 in HER2 positive HP positive group, 100 in HER2 negative HP negative group and 67 in HER2 negative HP positive group. No correlation was found between HP and HER2 status ($p = 0.314$). In addition, there was no relationship between HP status and the age, gender, histopathologic diagnosis, tumor location, TNM stage, ECOG performance status, grade, lymphovascular invasion, perineural invasion, and Lauren classification. Median OS of the entire population was 14.8 months (0.07-82.5). Median OS was 12.9 months (95% CI 7.7-18.0) in HP negative group and 27.4 months (95% CI 16.4-38.4) in HP positive group and the difference was statistically significant ($p = 0.046$).

Conclusions: Our results suggest that there is no relationship between HP infection and HER2 status in patients with GC. However, debate on this topic continues. Comprehensive prospective studies with larger series are required to clarify this relationship.

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Disclosure: All authors have declared no conflicts of interest.

652P Iron deficiency anemia in gastric cancer: A Canadian single site retrospective cohort study

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Background: Globally, gastric cancer is highly prevalent amongst men and women. While many studies have identified the prevalence and association of iron deficiency anemia (IDA) in all cancer patients, few have focused on the gastric population. We aimed to determine the proportion of patients with gastric cancer who developed IDA, chemotherapy induced anemia (CIA), and to identify types and frequencies of IDA therapies.

Methods: A retrospective study was carried out in 127 consecutive gastric cancer patients from 2006 to 2016 at St. Michael's Hospital, Toronto, Canada. Patient demographics, previous history of IDA, and IDA-based therapies were reviewed. IDA was defined as hemoglobin (Hb) <130 g/L in men and <120g/L in women and iron deficiency was defined as a transferrin saturation <20%. Pairwise deletion method was used for missing data. SAS 9.3 was used for data analysis.

Results: Of the 127 patients (median age 70 [interquartile range (IQR): 59-77]), 64.6% (82/127) were male. Most patients were diagnosed as stage III with a mean Hb of 119 g/L (standard deviation (SD): 20.2 g/L). Only 18.1% (23/127) patients had a history of IDA, 44.4% (20/45) had IDA at the time of gastric cancer diagnosis, and 59.1% (75/127) were anemic. Of the 127 patients, 16.5% had open surgery, while 45.7% had laparoscopic surgery. A total of 78 patients received chemotherapy, and of these 61 (78.2%) developed CIA. At last follow-up, 38.7% (24/62) patients developed IDA, and 79.5% (101/127) were anemic. Red blood cell (RBC) transfusions were most frequently prescribed (49.1%; median 4 units, IQR: 2-6.5), compared to oral (31.5%) or IV iron (16.5%) therapy.

Conclusions: There was a high proportion of IDA (38.7%) in our gastric cancer population despite inconsistent screening for ID. The incidence of anemia increased by 20% from the time of gastric cancer diagnosis to last follow-up. Approximately half of the patients received a RBC transfusion during their care. Our findings highlight the need for targeted therapy for ID to reduce RBC transfusion risk and to improve health-related quality of life. In response to our findings, we have implemented a quality improvement initiative that involves screening of iron status and provision of IV iron given limited oral absorption of iron in gastric cancer patients.

Legal entity responsible for the study: St. Michael's Hospital

Funding: None

Disclosure: All authors have declared no conflicts of interest.

653P Is surgical resection beneficial in recurrent or metastatic gastric cancer?

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Background: Although chemotherapy is currently established as a standard treatment in recurrent or metastatic gastric cancer, the role of palliative surgical resection is still controversial. We investigated the survival benefit of surgical resection in patients (pts) with recurrent or metastatic gastric cancer who received systemic chemotherapy.

Methods: A retrospective review was conducted on 696 pts who received palliative chemotherapy for recurrent (n = 307) or primary metastatic (n = 389) gastric cancer. Overall survival (OS) of pts who underwent surgical resection followed by chemotherapy was compared to that of pts who received chemotherapy alone.

Results: Among 138 pts (primary metastatic: 96, recurrent: 42) with surgical resection, gastrectomy, metastasectomy, and gastrectomy with metastasectomy were performed in 83 (primary metastatic: 81), 42, and 13 pts, respectively. Higher surgical resection rate was observed in pts with young age (<70) ($p = 0.005$), ECOG PS 0 or 1 ($p = 0.010$), primary metastatic ($p < 0.0001$), absence of liver metastasis ($p = 0.003$), and signet ring cell histology ($p = 0.002$). The median OS of pts who underwent surgical resection before chemotherapy was significantly longer than that of pts who received chemotherapy alone (19 vs. 9 months, $p < 0.0001$). The OS benefit of surgical resection was consistent across subgroups in terms of baseline characteristics. In multivariate analysis, surgical resection was independently associated with favorable OS (hazard ratio=0.41, $p < 0.0001$) along with ≥second-line chemotherapy ($p < 0.0001$), while

ECOG PS 2 or 3 ($p = 0.015$), signet ring cell histology ($p < 0.0001$), and peritoneal metastasis ($p = 0.038$) were independent prognostic factors of poor OS. In addition, the median OS of pts who underwent complete resection ($n = 61$) was significantly longer than that of pts who underwent incomplete resection ($n = 77$) (29 vs. 15 months, $p = 0.005$).

Conclusions: The present study suggests that judicious use of surgical resection before chemotherapy in recurrent or metastatic gastric cancer pts may result in favorable outcome, although large scale phase III trials are essential to establish this treatment approach as a standard practice.

Legal entity responsible for the study: Ajou University School of Medicine

Funding: Samyang Biopharmaceuticals Corporation, Korea

Disclosure: All authors have declared no conflicts of interest.

654P Nomograms for pre- and post- operative prediction of long-term survival for patients of proximal gastric cancer: A large-scale, single-centre retrospective study

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Background: The prognostic prediction for long-term survival for patients of proximal gastric cancer has not been well established.

Methods: Between December 2006 and June 2013, we prospectively collected and retrospectively analyzed the medical records of 746 patients with upper-third gastric cancer (GC). The data were split 75/25, with one group used for model development and the other group used for validation testing. COX regression was used to identify preoperative and postoperative risk factors associated with OS.

Results: Among the 746 patients examined, the 1-, 3- year overall survival rate is respectively: 89.4%, 66.1%. The preoperative T staging (cT), preoperative N staging (cN), ASA score, preoperative CA199, preoperative tumor size and the weight loss of 3-6 months were incorporated into the preoperative nomogram for overall survival (OS) prediction for the training set. In addition to these variables, LVI, postoperative tumor size, postoperative T stage, postoperative N stage, postoperative blood transfusion and postoperative complications were incorporated into the postoperative nomogram. All calibration curves for probability of OS fitted well. In the training cohort, the preoperative nomogram achieved a C-index of 0.751[95% confidence interval (CI) 0.732-0.770] in predicting OS and accurately stratified patients into 4 prognostic subgroups (5-year OS rates: 86.8%, 73.0%, 43.72% and 20.9%, $P < 0.001$). The postoperative nomogram had a C-index of 0.758 in predicting OS and accurately stratified patients into 4 prognostic subgroups (5-year OS rates: 82.6%, 74.3%, 45.9% and 18.9%, $P < 0.001$).

Conclusions: The 2 nomograms showed accurate pre- and postoperative prediction for long-term survival for patients of proximal gastric cancer.

Legal entity responsible for the study: Changming Huang

Funding: None

Disclosure: All authors have declared no conflicts of interest.

655P Safety of neoadjuvant/adjuvant chemotherapy for gastroesophageal cancers: A single cancer centre experience

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Background: Neoadjuvant/adjuvant chemotherapy for gastroesophageal cancers leads to improvement in overall survival and is currently a standard practice. We performed a retrospective study at the Clatterbridge Cancer Centre to examine its safety and identify risk factors.

Methods: Patients with gastroesophageal cancers who received cisplatin/5-FU based neoadjuvant and/or adjuvant chemotherapy were identified from electronic records. We looked at the number of emergency hospital admissions and death events within 30 days from receiving chemotherapy. Information was collected from hospital registry data and medical notes. We also looked at performance status (PS) (0/1 versus ≥ 2) and age (continuous variable) as potential factors for predicting the risk of death.

Results: We identified 1121 patients May 2002- Feb 2015. 73% were male; PS 0-1 in 91%, 2 in 6% and unknown in 3%; median age 64 years (16-81). 62% received cisplatin/5FU or cisplatin/capecitabine (as in the OEO2 Trial) and 38% received epirubicin/cisplatin/capecitabine (as in the MAGIC Trial). Mortality data was available for all patients whereas admission data was available for only 360 patients. There were 98 30-day admissions and these affected 83 patients (23%). The 3 most common causes for admissions were: Gastrointestinal toxicities 45%, infection 15% and vascular events 10%. There were 31 30-day death events (2.8%). There was no difference in mortality rates according to PS but older age was associated with a higher incidence of death (Mann-Whitney test: $P = 0.002$). The median age for patients who died within 30 days from chemotherapy was 69 years. The group of patients ≥ 70 years (26% of the study population) had an odds ratio of 2.37 for dying compared with patients < 70 years.

Conclusions: In our experience, mortality rate after neoadjuvant/adjuvant chemotherapy for gastroesophageal cancers was similar to that reported in landmark studies: In OEO2 3% of patients died before surgery and in MAGIC 1.6% died within 60 days from chemotherapy. PS did not seem to predict risk of death but this can be attributed to the good selection of patients as only 6% had a PS of 2. Patients ≥ 70 years had a higher risk of death and this should be taken into consideration when assessing patients for chemotherapy.

Legal entity responsible for the study: Clinical Effectiveness Department, The Clatterbridge Cancer Centre NHS Foundation Trust

Funding: None

Disclosure: All authors have declared no conflicts of interest.

656P Peritoneal lavage CEA mRNA levels predict conversion gastrectomy outcomes after induction chemotherapy in gastric cancer patients with peritoneal metastasis

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Background: The outcome of gastric cancer patients with peritoneal metastasis remains poor. We treated these patients with intraperitoneal and intravenous administration of paclitaxel plus oral tegafur/gimeracil/oteracil (S-1), followed by gastrectomy in responders. However, it remains to be determined whether gastrectomy contributes significantly to the survival benefit in good responders. It is also unclear how and when gastrectomy should be performed. Therefore, reliable biomarkers are urgently needed to predict the outcome of gastrectomy. Herein, we evaluated the clinical significance of carcinoembryonic antigen (CEA) mRNA levels in peritoneal lavage as a biomarker for the indication of conversion gastrectomy.

Methods: The peritoneal lavage of 68 patients who received the above regimen as induction chemotherapy was repeatedly collected via intraperitoneal access ports. Gastrectomy was considered when improvement of peritoneal metastasis was confirmed by a second laparoscopic examination with negative peritoneal cytolog. CEA and porphobilinogen deaminase (PBGD) mRNAs were chronologically quantified using the transcription reverse-transcription concerted reaction method. The CEA-mRNA Index (CmRI) was calculated as CEA mRNA/PBGD mRNA x 10,000.

Results: Thirty-nine patients received gastrectomy and 29 patients did not (median survival time (MST): 27.8 vs. 10.7 months, $P < 0.001$). In the gastrectomy-positive group, the outcome largely differed according the CmRI immediately prior to surgery. Patients ($n = 20$) who had a preoperative CmRI value of < 100 were associated with a significantly longer MST compared to patients ($n = 19$) who had a preoperative CmRI value of > 100 (41.8 vs. 20.8 months, $P < 0.001$). A preoperative CmRI value of < 100 was an independent predictor of survival for gastrectomy-positive patients in the multivariate analysis.

Conclusions: The CmRI reflects the response of peritoneal metastases to induction intraperitoneal chemotherapy. It may be a useful biomarker to determine gastrectomy in gastric cancer patients with peritoneal metastasis.

Legal entity responsible for the study: Hironori Yamaguchi

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Disclosure: All authors have declared no conflicts of interest.

657P Nutritional recovery after open and laparoscopic distal gastrectomy for early gastric cancer: A prospective multicenter comparative trial (CCOG1204)

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Background: Little information from prospective clinical trials is available on the influences of surgical approaches on postoperative body compositions and nutritional status. We designed a prospective non-randomized trial to compare postoperative

chronological changes in body composition and nutritional status between laparoscopic and open distal gastrectomy for stage I gastric cancer (GC).

Methods: Body compositions and nutritional indicators in blood tests were measured at the baseline and at the 1st, 3rd, 6th and 12th postoperative months (POM). The primary endpoint was the decrease relative to the baseline in the body muscle mass at POM6.

Results: Ninety-six patients for the laparoscopic group and 52 for the open group were eligible for data analysis. No significant differences were found in any baseline demographics, body compositions and nutritional indicators between the groups. The changes of body muscle mass at POM 6 were similar in both groups. Overall, no significant differences between the groups were observed in any of the body composition and nutritional indicators during the first year after surgery.

Conclusions: Postoperative body compositions and nutritional status was not affected by surgical approaches during the first 12 months after surgery in patients who underwent distal gastrectomy for stage I GC.

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Legal entity responsible for the study: None

Funding: None

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658P Randomized, controlled Phase III trial comparing 3D and 2D laparoscopic gastrcetomy for gastric cancer

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Background: To determine the safety and superiority of three-dimensional (3D) laparoscopic gastrectomy (LG) compared with two-dimensional (2D) laparoscopic in patients with gastric cancer.

Methods: A large-scale, phase 3, prospective randomized controlled trial was conducted. The primary end point was operation time. Morbidity within 30 postoperative days and surgical outcomes were compared to evaluate the safety and efficacy of 3D LG as a secondary end point.

Results: A total of 438 patients were randomized (3D group 219 cases; 2D group 219 cases) between January 1, 2015 and April 1, 2016. Nineteen patients were excluded. Finally, a total of 419 patients were analyzed (3D group 211 cases, 2D group 208 cases). There were no significant differences between the two groups regarding the operation time (3D vs 2D, 175.52±35.53 min vs 173.63±37.00 min, $p = 0.596$). The operation time was further stratified analysis by BMI and operative region which showed that when BMI is larger than 25kg/m2 the 3D group in the Splenic Hilar regional lymph node cleaning time was significantly lower than the 2D group (29.4±7.8 min vs 23.3±6.4 min, $p = 0.024$). The intra-operative blood loss in the 3D group was significantly lower than the 2D group (61.37±82.99 ml vs 81.54±119.44 ml, $P = 0.045$). Furthermore analysis suggested that 3D laparoscopic was a protect factor for excessive blood loss (≥200ml). The postoperative complication rates of the 3D and 2D groups were 17.1% (36/211) and 13.9% (29/208), respectively, $p = 0.378$. No patients died during the postoperative hospital stay. Postoperative questionnaire survey showed that the surgeon experienced better depth perception with the 3D system and there was no significant difference in postoperative strain between the two groups.

Conclusions: 3D LG not only can significantly reduce the lymph node dissection time at complicated regional, but also has a benefit of less intra-operative blood loss and lower occurrence of excessive bleeding incidence compared with conventional 2D surgery. (Number NCT02327481)

Legal entity responsible for the study: Changming Huang

Funding: None

Disclosure: All authors have declared no conflicts of interest.

659P Anthracycline-based triplets do not improve the efficacy of platinum-fluoropyrimidine doublets in advanced gastric cancer: AGAMENON study data

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Background: Although anthracycline-based triplets are one of the most widely used regimens for the treatment of advanced gastric cancer (AGC), the incremental benefit associated with the inclusion of anthracyclines in therapeutic combinations is unknown. The aim of this study is to evaluate the efficacy and tolerance of epirubicin triplets vs platinum-fluoropyrimidine doublets in a national AGC registry.

Methods: We recruited patients with AGC treated at 28 Spanish centers with polychemotherapy, without trastuzumab, from 2008 to 2016. The effect of anthracycline-based triplets was assessed by propensity score matching (PSM) and Cox proportional hazards (PH) regression.

Results: 1002 patients (doublets, $n = 653$, triplets with anthracyclines, $n = 349$) were included. In the multivariate Cox PH regression model, there was no significant increase in OS in favor of anthracycline-based triplets: HR 0.90 (95% CI, 0.78-1.05), $p = 0.20035$. After PSM, the sample contains 325 pairs with similar baseline characteristics. There was also no increase of OS with this method: 10.5 (95% CI, 9.7-12.3) vs. 9.9 (95% CI, 9.2-11.4) months, HR 0.91 (CI 95%, 0.76-1.083), (stratified log-rank test, $p = 0.226$), for doublets without anthracyclines vs anthracycline-based triplets. Objective responses were higher with triplets: 32.9% vs. 24.0% ($p = 0.014$) without significant differences in PFS: HR 0.95 (CI 95%, 0.80-1.13), stratified log-rank test, $p = 0.873$. Triplets were associated with higher hematological toxicity, and increased toxicity-related admissions by 86%. The addition of epirubicin is viable, but 23.7% discontinued treatment because of adverse effects or patient decision.

Conclusions: Anthracycline triplets increased the antitumor effect (objective responses) of the treatment. However, they were not associated with an incremental benefit in PFS or OS and instead had a higher toxicity.

Legal entity responsible for the study: Paula Jimenez Fonseca

Funding: None

Disclosure: All authors have declared no conflicts of interest.

660P First-in-human study of IMAB362, an anti-claudin 18.2 monoclonal antibody, in patients with advanced gastroesophageal cancer

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Background: Claudin 18.2 (CLDN18.2), a gastric mucosa tight junction protein, is aberrantly expressed in various cancers. IMAB362, an anti-CLDN18.2 monoclonal antibody, specifically binds to CLDN18.2-positive cancer cells. This first-in-human (FIH), dose-escalation study evaluated the clinical effects of IMAB362 in patients with advanced gastroesophageal cancer (GEC) after a single IV infusion.

Methods: This phase 1 study (NCT00909025), conducted at 6 centers in Germany and Latvia, enrolled patients (≥18 yrs) with advanced GEC into 5 sequential dose-escalations cohorts (33, 100, 300, 600, 1000 mg/m^2) that followed a 3 + 3 design. Safety/tolerability, including determination of maximum tolerated dose (MTD) based on emergence of dose-limiting toxicities (DLTs), was the primary objective; secondary objectives included assessment of the IMAB362 pharmacokinetic (PK) profile, immunogenicity, and antitumor activity (assessed by RECIST v1.0).

Results: All 15 enrolled patients (median age 61.3 years [range: 46–76]) had received ≥1 prior chemotherapy with nearly half ($n = 7/15$; 47%) having undergone previous radiotherapy. All IMAB362 doses tested were generally well tolerated; as no DLT was

observed within 4 weeks of treatment the MTD was not established. Mild-to-moderate gastrointestinal disorders (eg, nausea, vomiting) were the most common treatment-related adverse events (AEs); however, no clear dose dependency was observed. Neither of the 2 serious AEs (grade 2 odynophagia [300 mg/m^2]; grade 3 urinary retention [600 mg/m^2]) was considered treatment related. No antibodies against IMAB362 were detected. Most patients (n = 12/15; 80%) showed progressive disease at Weeks 4–5 after a single IMAB362 IV infusion; however, 1 patient in the 600 mg/m^2 dose group had stable disease for ~2 months postinfusion. The linear, dose-proportional PK profile supports IMAB362 dosing at 300–600 mg/m^2 every 2 weeks.

Conclusions: Single-dose administration of IMAB362 was well tolerated up to 1000 mg/m^2 in this FIH dose-escalation study. These results encourage further clinical testing of IMAB362 in patients with CLDN18.2-positive GEC.

Clinical trial identification: NCT00909025, May 18, 2009

Legal entity responsible for the study: Ganymed Pharmaceuticals AG, A company of Astellas Pharma, Inc.

Funding: Ganymed Pharmaceuticals AG, A company of Astellas Pharma, Inc.

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661P Bidirectional chemotherapy in gastric cancer (GC) with peritoneal carcinomatosis (PC) combining intravenous chemotherapy with pressurized intraperitoneal aerosol chemotherapy (PIPAC): Results of 103 procedures in 52 patients

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Background: Up to 43% of GC patients show synchronous PC at time of diagnosis and peritoneal relapse develops in 10–46% of cases after radical surgery. Systemic chemotherapy shows low response rate (14-25%) and median survival of 8-10 months. Innovative therapeutic approaches are needed to improve survival.

Methods: Treatment protocol for untreated patients included initial staging laparoscopy/laparotomy, 3–4 courses of systemic chemotherapy (XELOX) followed by Pressurized IntraPeritoneal Aerosol Chemotherapy (PIPAC) with low-dose Cisplatin and Doxorubicin every 6 weeks until progression of disease or death. Criteria of progression were 50% and more PCI increase or distant metastases. Patients with primary or recurrent GC, who received earlier one or two lines of systemic chemotherapy, didn't receive 4 XELOX courses before PIPAC. Primary endpoints were overall survival and pathologic response after peritoneal rebiopsy.

Results: 52 patients were included (15 men, 37 women, mean age 53.5 years), 38 patients had primary GC with PM and 14 had peritoneal relapse after surgery (with or without adjuvant therapy). 19 patients had systemic chemotherapy before inclusion to the program. Mean PCI was 12.6 (min-max 3-34). Altogether, 103 PIPAC procedures were performed in the 52 patients. The main reason for not undergoing more than one PIPAC was PC progression (16). Pathological response was estimated in 30 pts underwent more than 1 PIPAC. 33% of patients showed complete pathologic response (CR), 50% - PR and 17% of cases had weak or no response. PCI score has decreased in 37% of patients, remained stable in 10% and has increased in 53% of cases. Thus PCI change isn't equal to the pathologic response. Median survival was 14.6 months and one-year overall survival was 62%. The median survival was better in patients with low PCI and in those who responded to systemic chemotherapy, but the difference was not significant.

Conclusions: Bidirectional chemotherapy combining intravenous chemotherapy and PIPAC can induce objective tumor regression and is associated with a promising survival in GC with PC.

Legal entity responsible for the study: P.A. Herzen Moscow Oncology Research Institute - Branch of the National Medical Research Radiological Center, Ministry of Health of the Russian Federation, Moscow, Russian Federation

Funding: None

Disclosure: All authors have declared no conflicts of interest.

662P Gastrectomy after response to intraperitoneal and systemic chemotherapy for gastric cancer with peritoneal metastasis or positive peritoneal cytology

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Background: The prognosis of gastric cancer patients with peritoneal metastasis (P1) or positive peritoneal cytology (CY1) remains poor in spite of recent progress in systemic chemotherapy. We developed several regimens combining intraperitoneal (IP) and systemic chemotherapy, and evaluated the safety and efficacy in clinical trials. Gastrectomy after response to combination chemotherapy is a promising option for P1 or CY1 gastric cancer. A retrospective study was performed to evaluate this multidisciplinary treatment strategy.

Methods: This study enrolled 158 primary P1 or CY1 gastric cancer patients treated with IP paclitaxel or docetaxel with systemic chemotherapy at the University of Tokyo Hospital between 2005 and 2015. Gastrectomy was performed when peritoneal cytology turned negative, and the disappearance or obvious shrinkage of peritoneal metastasis was confirmed by laparoscopy. Combination chemotherapy was restarted after surgery and repeated with appropriate dose reduction.

Results: Ninety-one patients were chemo-naïve, and 67 patients had received standard systemic chemotherapy at the previous hospitals before the initiation of IP chemotherapy. Gastrectomy was performed in 94 (P1 85, P0CY1 9) of 158 (P1 147, P0CY1 11) patients after response to chemotherapy. R0 resection was achieved in 61 of 94 patients (65%). Postoperative complications included anastomotic leakage in 3 patients and pancreatic fistula in 2 patients, which were cured conservatively. The median survival time (MST) of 94 patients with gastrectomy was 31.3 months (95% confidence interval [CI] 26.1-39.3 months) from the initiation of IP chemotherapy and 35.8 months (95% CI 28.5-40.1 months) from the diagnosis of gastric cancer. Relapse or progression was observed in 78 of 94 patients with a median time of 17.9 months (95% CI 15.0-24.2 months). The first site of recurrence or progression was the peritoneum in 61 patients and the other site in 28 patients (both in 11 patients). The MST of 64 patients without gastrectomy was 12.3 months (95% CI 10.0-13.9 months).

Conclusions: Gastrectomy after response to intraperitoneal and systemic chemotherapy is safe and may prolong the survival of P1 and CY1 gastric cancer patients.

Legal entity responsible for the study: The University of Tokyo

Funding: Japan Agency for Medical Research and Development

Disclosure: All authors have declared no conflicts of interest.

663P Change in the molecular profile of tumor tissues during treatment with trastuzumab, as analyzed by next-generation sequencing and immunohistochemistry: A multicenter prospective biomarker study on HER2-positive gastric cancer

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Background: Trastuzumab (Tmab) is an active molecular-targeted drug for HER2-positive gastric cancer (GC) patients. However, continued use of Tmab beyond progression is not established in HER2-positive GC, unlike that of breast cancer. Therefore, we conducted this study to evaluate the resistance mechanism of anti-HER2 drugs in metastatic GC patients.

Methods: Metastatic HER2-positive GC patients treated with Tmab were registered prospectively, and tumor tissues were obtained by biopsy from primary lesions at the following points: (1) pre-treatment, (2) post-treatment, and (3) disease progression during chemotherapy with Tmab. Formalin-fixed paraffin-embedded tissue slides were prepared, and the expression of receptor tyrosine kinases (RTKs) such as EGFR, HER2, HER3, c-MET, FGFR2 and IGF-1R was evaluated by immunohistochemistry (IHC). Hot spot mutations and copy number variations (CNVs) were analyzed by next-generation sequencing (NGS) using Ion AmpliSeq Cancer Hotspot Panel v2.

Results: Twenty patients were enrolled and evaluated by IHC, and 15 of 20 patients were evaluated by NGS. One patient was excluded because HER2 status was revealed as negative after registration. HER2 expression (≥2+) by IHC have disappeared after treatment in 8 patients (42%). FGFR2 expression (≥2+) by IHC was most frequently

observed after treatment. Cases with IGF-1R expression (≥2+) were significantly increased after treatment ($p < 0.05$). Somatic mutations of *TP53* (n = 9), *KRAS* (n = 2), *BRAF* (n = 2), *SMAD4* (n = 1), *CDH1* (n = 1), and *CDKN2A* (n = 1) were observed before treatment. Mutations of *TP53* (n = 2), *KRAS* (n = 2), *PIK3CA* (n = 2), *CDH1* (n = 2), *PDGFRA* (n = 1), and *PTEN* (n = 1) were newly observed during the treatment. CNV analyses revealed that the cases with gain of *KRAS* and loss of *STK11* were likely to increase during treatment with Tmab.

Conclusions: Our study indicated that molecular changes in RTK expression and genomic alternation frequently occur during treatment with Tmab. These findings will contribute to the development of individualized treatment for HER2-positive GC patients.

Clinical trial identification: UMIN000006454 (Japan). Release date is 03/October/2011.

Legal entity responsible for the study: National Cancer Center, Tokyo

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Disclosure: All authors have declared no conflicts of interest.

664P Phase 1 Study of IMAB362 with immunomodulation in patients with advanced gastric cancer

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Background: IMAB362, a monoclonal antibody to Claudin 18.2 (CLDN18.2), has demonstrated strong tumor cell killing activity via antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) in preclinical gastric cancer models. Safety/tolerability, pharmacodynamics (PD), and clinical response of IMAB362 in combination with zoledronic acid (ZA) and interleukin-2 (IL-2), which expand and activate ADCC-mediating gamma9delta2 T cell effector populations, was assessed in patients with advanced upper GI adenocarcinomas.

Methods: This open-label phase 1 exploratory study (NCT01671774) enrolled heavily pretreated patients (age ≥18 yrs) whose tumor cells had CLDN18.2 staining intensity either 2+ in ≥ 40% cells or any 3+ by IHC. Patients were enrolled into 1 of 4 treatment arms: Arm 1, IMAB362 + ZA; Arm 2, IMAB362 + ZA + 1 million IU (mIU) IL-2; Arm 3, IMAB362 + ZA + 3 mIU IL-2; Arm 4, IMAB362 alone. Patients received: IV IMAB362 Q3W, 800 mg/m^2 on Cycle 1, Day 1 and 600 mg/m^2 on Day 1 of every subsequent cycle; IV ZA 4 mg, Day 1 of Cycles 1 and 3; subcutaneous IL-2, Days 1–3 of Cycles 1 and 3. Safety/tolerability of IMAB362, immune cell phenotyping by flow cytometry and IMAB362-induced ADCC in a cytotoxicity assay were primary endpoints; clinical response (per RECIST v1.1) was a secondary endpoint.

Results: Of the 29 enrolled patients, 28 received treatment (Arm 1, n = 7; Arm 2, n = 9; Arm 3, n = 7; Arm 4, n = 5), 21 were in the PD analyses, and 19 in response analyses. IMAB362 had acceptable safety/tolerability unaltered by immunomodulation; grade 1–4 nausea and vomiting (both n = 15/28; 54%) were the most common adverse events. Expansion and activation of gamma9delta2 T cells and activation of NK cells were initiated by all treatment arms; however, these effects were more extensive in pts treated with IMAB362 + ZA/IL-2 (n = 10 [5 each in Arms 2 and 3]). A strong ADCC in response to IMAB362 was observed in most patients; however, ADCC kinetics over time and dependency on ZA/IL-2 were not conclusive. No patient achieved confirmed response; 11 (58%) had confirmed stable disease.

Conclusions: This study provided encouraging data on safety/tolerability and cytotoxicity of IMAB362 in combination with ZA/IL-2. Objective responses were not observed.

Clinical trial identification: NCT01671774, August 21, 2012

Legal entity responsible for the study: Ganymed Pharmaceuticals, A company of Astellas Pharma, Inc

Funding: Ganymed Pharmaceuticals, A company of Astellas Pharma, Inc

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665P Modified Glasgow prognostic score, prognostic nutritional index and ECOG score could be new prognostic factors for survival in metastatic gastric cancer

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Background: Metastatic gastric carcinoma (MGC) patients usually present with cachexia and sarcopenia. We aimed to analyze the prognostic values of the sarcopenia index (SI), cachexia index (CI) and inflammatory indexes (advanced lung cancer inflammation index [ALI], modified Glasgow Prognostic Score [mGPS], prognostic index [PI], prognostic nutritional index [PNI] and neutrophil-to-lymphocyte ratio [NLR]) on MGC at presentation.

Methods: A retrospective study was performed in 87 patients with MGC. SI, CI, PI, PNI, ALI, mGPS and NLR was measured and calculated appropriately. Due to lack of studies from our country, SI cutoff value has been obtained by using both western (EGWSOP) and eastern (Harada Y, et al) sources separately. Statistical analysis has been done by SPSS.

Results: Median follow-up time was 9 months (range 1-64) and 78 patients died during follow-up. Fiftynine patients were male (63%) and median age was 62 (23-88). According to univariate analysis these factors had significant negative impact on general survival (GS): increased leukocyte ($p = 0{,}003$) and neutrophile ($p < 0{,}001$), decreased lymphocyte count ($p = 0{,}048$), increased CRP ($p < 0{,}001$) and decreased serum albumin ($p < 0{,}001$), high mGPS ($p < 0{,}001$) and PI score ($p < 0{,}001$), PNI level <45 ($p < 0{,}001$), NLR level ≥ 3,41 ($p < 0{,}001$), ALI level <18 ($p < 0{,}001$), CI level under 35 ($p < 0{,}001$), SI (Harada Y, et al) ≤44,5 for males and ≤36,5 for females ($p = 0{,}003$), ECOG score ≥ 2 ($p < 0{,}001$), weight loss more than 10% during last 6 months ($p = 0{,}002$), BMI under 24 ($p = 0{,}009$). According to multivariable analysis mGPS (HR 2,494, 95% CI 1,25–4,94 $p = 0{,}02$), PNI (HR 4,2, 95% CI 1,73–10,1 $p < 0.001$) and ECOG score (HR 1,541, 95% CI 1,089-4,214, $p = 0.004$) were independent prognostic factors on GS. mGPS was found to be more valuable than other indexes for predicting mortality. The time consumed during these tests were: m GPS 10 sec, PNI 20 sec, PI 15 sec, NLR 15 sec, ALI 40 sec, CI 17 min, SI 15 min.

Conclusions: On our study; mGPS, PNI and ECOG score were independent indicators for shorter survival. mGPS and PNI, which can be calculated by using only CRP, albumin levels and complete blood counts, might be inexpensive, practical and beneficial in routine clinical practice.

Legal entity responsible for the study: Marmara University Pendik Treatment & Research Hospital, Medical Oncology Department

Funding: None

Disclosure: All authors have declared no conflicts of interest.

666P Accuracy and prognostic significance of oncologists' estimates and scenarios for survival time in a randomised Phase 2 trial of regorafenib in advanced gastric cancer

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Background: We have proposed that best, worst and typical scenarios for survival, based on simple multiples of an individual's expected survival time (EST) estimated by their oncologist, are a useful way of formulating and explaining prognosis in advanced cancer. We aimed to determine the accuracy and prognostic significance of such estimates in a multicentre, randomized trial.

Methods: 66 oncologists estimated the EST at baseline for each of 152 participants in the INTEGRATE trial. We expected oncologists' estimates of EST to be well calibrated

(∼50% of patients living longer or shorter than their EST) and imprecise (<33% living within 0.67 to 1.33 times their EST), but to provide accurate scenarios for survival time (∼10% dying within a quarter of their EST, ∼10% living longer than 3 times their EST and ∼50% living for half to double their EST). We also hypothesized that oncologists' estimates of EST would be independently predictive of overall survival in a multivariable Cox model including conventional prognostic factors and health related quality of life.

Results: Oncologists' estimates of EST were well calibrated (45% shorter than observed), imprecise (29% lived within 0.67 to 1.33 times observed), and moderately discriminative (Harrell C-statistic 0.62, P = 0.001). Scenarios derived from oncologists' estimates were remarkably accurate: 9% of patients died within a quarter of their EST, 12% lived longer than three times their EST and 57% lived within half to double their EST. Oncologists estimates of EST (in months) were independently significant predictors of overall survival (HR = 0.89, 95% CI 0.83 to 0.95, P = 0.001) in a Cox model including ECOG performance status, primary site, number of metastatic sites, neutrophil to lymphocyte ratio≥ 3, treatment group, age, and the EORTC QLQC30 physical function score.

Conclusions: Oncologists' estimates of survival time were well calibrated, moderately discriminative, and independently significant predictors of overall survival. Best, worst and typical scenarios for survival based on simple multiples of the EST were remarkably accurate and would provide a useful method for estimating and explaining prognosis in this setting.

Legal entity responsible for the study: NHMRC Clinical Trials Centre

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667P ERBB3 mutations in advanced gastric signet-ring cell carcinoma (SRCC) and the implications for targeted therapy

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Background: Studies have shown that ERBB3 mutations are associated with poor clinical prognosis by increasing the rate of metastasis and recurrence in many cancers. ERBB3 targeted therapeutics can be effective against ERBB3 mutant-driven tumors. ERBB signal pathway plays a very important role in the initiation and progression of gastric cancer, however the ERBB2 expression and mutation rate is relative low especially in gastric SRCC. Thus, ERBB3 might be a promising target for the treatment in SRCC patients. The aim of this study is to speculate the prognostic and targeted therapy value in gastric SRCC by evaluating the mutation rate and type of ERBB3.

Methods: 92 patients with histological diagnosis of advanced gastric SRCC were retrospectively selected for this study. ERBB3 mutation was evaluated by next generation sequencing from formalin-fixed paraffin-embedded (FFPE) samples. ERBB2 expression was tested by immunohistochemistry. Correlations between ERBB2/3 status and clinical pathologic characteristics and overall survival (OS) were performed.

Results: All of the 92 patients were diagnosed as local advanced or metastatic gastric SRCC (92.4% were stage III, 7.6% were stage IV). All the patients received 5-FU-based first-line chemotherapy. 14 out of all 92 patients were ERBB3 mutated SRCC, 12 of all the 14 mutations were in the extracellular domain, 2 were in the transmembrane region. There was no correlation between ERBB3 mutation and serosa invasion (P = 0.389) or lymph node metastasis (P = 1.000). The median OS was 20.5 months (95% CI = 10.05to 30.95 months) for patients with ERBB3 mutation, and 19.0 months (95% CI = 15.54 to 22.46 months) for patients without ERBB3 mutation (P = 0.567). There was no difference in OS according to HER2 positive or negative in ERBB3 mutated patients (14.8 months vs 20.5 month, P = 0.374).

Conclusions: Our study demonstrated 15.2% of gastric SRCC patients harboring ERBB3 mutation, providing a potential subgroup of gastric SRCC for targeted treatment on ERBB pathway. No difference of OS was observed, probably due to the relative small sample size and low ERBB2 positive rate in SRCC patients. Further investigation on ERBB3 is warranted to clarify mechanisms of ERBB pathway in gastric SRCC.

Legal entity responsible for the study: The Comprehensive Cancer Centre of Drum Tower Hospital, Medical School of Nanjing University & Clinical Cancer Institute of Nanjing University, Nanjing 210008, China

Funding: None

Disclosure: All authors have declared no conflicts of interest.

668P Estimating 12-weeks life expectancy in metastatic gastric cancer (mGC) patients (pts) candidates for second-line treatment: The "Gastric Life" nomogram

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Background: The estimation of life expectancy of mGC pts in the second-line setting may be biased by the absence of objective prognostic tools to be used for enrollment in clinical trials and for decision making in the daily practice. The availability of evidence-based second-line treatment options highlights the need of nomograms/prognostic scores which may assist clinicians in refining pts' clinical selection in the salvage setting. The aim of this study was to build a nomogram for predicting the individual 12-weeks overall survival (OS) of mGC pts starting a second-line treatment.

Methods: At 26 Italian Institutions, 320 mGC patients receiving second-line chemotherapy, ramucirumab or paclitaxel-ramucirumab were used as developing set. Putative prognostic variables (age, gender, ECOG PS, T resection, Lauren's histotype, primary anatomic site, synchronous presentation, number and location of metastatic sites, PFS and response to 1-line, LDH, neutrophils/lymphocytes ratio) were selected using a random forest model and included in a Cox multivariable model from which the nomogram was derived. The nomogram performance was evaluated by means of calibration plot and discriminative ability (Harrell's C index).

Results: Three variables were selected and included in the nomogram: ECOG PS (P < 0.0001), neutrophils/lymphocytes ratio (P < 0.0001) and peritoneal involvement (P = 0.0005). The model discriminative ability index was 0.858. The internal calibration plot did not show significant differences between observed and predicted 12-weeks OS probabilities. External validation analysis is currently ongoing.

Conclusions: Our nomogram may be a useful tool to predict 12-weeks life expectancy in mGC pts candidates for second-line therapy. Based on 3 easy-to-collect variables, the" Gastric Life" nomogram may improve second-line pts' selection and assist researchers for the enrollment in clinical trials.

Legal entity responsible for the study: Filippo Pietrantonio

Funding: None

Disclosure: All authors have declared no conflicts of interest.

669P TG01/GM-CSF and adjuvant gemcitabine in patients with resected RAS-mutant adenocarcinoma of the pancreas

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Background: The study evaluated the immune response, safety and clinical efficacy of the TG01/GM-CSF vaccine, an antigen-specific cancer immunotherapy consisting of 7 RAS peptides targeted to KRAS mutated pancreatic adenocarcinoma (PAC). The efficacy of adjuvant chemotherapy in resected disease is limited with 1- and 2-year published overall survival (OS) rates ranging from 56-80% and 30-54% respectively. TG01 induces RAS mutant-specific T-cell responses which are enhanced by co-administration of GM-CSF.

Methods: Patients (pts) were eligible after R0 or R1 PAC resection. As soon as possible after surgery, TG01 (0.7 mg intradermal injection (id)) together with GM-CSF (0.03 mg id) was given on days 1, 3, 5, 8, 15, 22 and 2-weekly thereafter until the end of gemcitabine (starting within 12 weeks of surgery and given for 6 cycles). Thereafter TG01/GM-CSF was given 4-weekly up to 1 yr and 12-weekly up to 2 yrs. Immune response was assessed using antigen-specific (TG01) Delayed-Type Hypersensitivity and T-cell proliferation. OS and disease free survival (DFS) was assessed from surgery; ∼8 weeks before first TG01 injection.

Results: To date, 19 pts (68% R1) have been followed for 2 1/2 yrs. Median CA19-9 was 15 (5, 240) U/ml at baseline. 8 SARs in 5 pts have occurred; 4 related to gemcitabine (anemia, pulmonary infection and 2 fever); 3 related to TG01/GM-CSF (2 anaphylaxes and 1 hypersensitivity); and 1 possibly related to all products (dyspnea). The allergic reactions only occurred after several cycles of gemcitabine and resolved within 1-2 hrs. There were no treatment related deaths. TG01 induce an immune response in 17/19 patients by week 11, which demonstrate that TG01 vaccination activate TG01 specific T-cells. OS rate at 2 yrs was 68.4 (95% CI 47.5, 89.3). OS rate at 2 1/2 yrs will be presented. Median OS was 33.1 months (95% CI 16.8, 40.1). Median DFS was 13.9 months (95% CI 5.4-21.0).

Conclusions: The regimen was generally well tolerated although some late, manageable allergic reactions were seen. OS and DFS was encouraging in view of published reports. TG01/GM-CSF generated early immune responses in 89% of patients with R0/R1 resected pancreatic cancer. 13 pts have been recruited in a modified dose cohort with 2 yrs data in 2Q 2018.

Clinical trial identification: NCT02261714.

Legal entity responsible for the study: Targovax ASA

Funding: Targovax ASA

Disclosure: T.J. Gjertsen, A-S. Møller: Share options in Targovax ASA. A-K. Aksnes: Stocks and share options in Targovax ASA. D. Palmer: Honoraria: Celgene, Nucana, Bayer, BMS. Consulting and advisory role: Celgene, Nucana, Bayer, BMS Research funding: Nucana, Bayer. All other authors have declared no conflicts of interest.

670P A randomized, double-blind, multi-center phase III study evaluating paclitaxel with and without RAD001 in patients with gastric or esophagogastric junction carcinoma who have progressed after therapy with a fluoropyrimidine/platinum-containing regimen (RADPAC)

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Background: There is a need for effective treatments in the second- or further line setting in advanced gastric cancer, especially for new agents. In the current trial we evaluated paclitaxel with RAD001 (everolimus) in patients with gastric carcinoma who have progressed after therapy with a fluoropyrimidine/platinum-containing regimen.

Methods: This is a randomized, double-blind, multi-center phase III study. Patients with gastric carcinoma or adenocarcinoma of the esophagogastric junction (EGJ) who have progressed after treatment with a fluoropyrimidine/platinum-containing regimen were randomly assigned to receive Paclitaxel (80 mg/m2) on day 1, 8 and 15 plus placebo (arm A) or RAD001 (10mg daily, arm B) d1-d28, repeated every 28 days as 2nd, 3rd or 4th line therapy. Primary end point was overall survival (OS), secondary endpoints were best overall response, disease control rate, progression free survival (PFS) and toxicity.

Results: 300 patients (median age: 62 years; median lines prior therapy: 2; 47.7% of patients had prior taxane therapy) were randomly assigned (Arm A, 150, Arm B, 150). In the intention to treat population, there was no significant difference in median PFS (placebo, 2.07 vs. RAD001, 2.2 months, HR 0.88, $p = 0.3$) or median OS (placebo, 5.0 vs. RAD001, 6.1 months, HR 0.93, $p = 0.54$). For patients with prior taxane use, RAD001 improved PFS (placebo 1.8 vs. RAD001, 2.7 months, HR 0.69, $p = 0.03$) and OS (placebo 3.9 vs. RAD001, 5.8 months, HR 0.73, $p = 0.07$). Combination of paclitaxel and RAD001 was tolerable, but the RAD001 arm was associated with significantly more grade 3-5 mucositis (13.3% vs. 0.7%; $p < 0.001$).

Conclusions: The addition of RAD001 to paclitaxel/RAD001 did not improve outcomes in pretreated metastatic gastric/EGJ cancer. Of note, activity was seen in the taxane pretreated group. Additional biomarker studies are planned to look for subgroups that may have a benefit.

Clinical trial identification: Protocol Code: CRAD001RDE35T clinicaltrials.gov NCT01248403

Legal entity responsible for the study: Krankenhaus Nordwest GmbH

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671P Interim safety and clinical activity of nivolumab (Nivo) in combination with S-1/capecitabine plus oxaliplatin in patients (pts) with previously untreated unresectable advanced or recurrent gastric/gastroesophageal junction (G/GEJ) cancer: part 1 study of ATTRACTION-04 (ONO-4538-37)

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Background: Nivo monotherapy demonstrated its efficacy with manageable safety for G/GEJ cancer refractory or intolerant to standard chemotherapy at the primary analysis (ATTRACTION-02[ONO-4538-12]: ASCO-GI 2017, Kang YK et al. J Clin Oncol. 2017; 35 [suppl 4S abstract 2]). This randomized phase 2/3 trial is to evaluate the efficacy and safety of Nivo in combination with 1st line chemotherapy in unresectable advanced or recurrent G/GEJ cancer (NCT02746796).

Methods: This trial includes previously untreated pts aged $\geq$ 20 years with ECOG PS 0-1 and had measurable, unresectable advanced or recurrent HER2 (-) G/GEJ cancer. It consists of 2 parts. Part 1 is a randomized, open-label trial to evaluate the feasibility of Nivo (360 mg, Q3W) in combination with oxaliplatin (130 mg/m^2, Q3W) plus either S-1 (40 mg/m^2 twice daily, day 1-14, SOX) or capecitabine (1000 mg/m^2 twice daily, day 1-14, CapeOX) in terms of activity and safety. Part 2 is a randomized, double-blind, placebo-controlled trial comparing Nivo to placebo in combination with SOX/CapeOX in terms of overall survival and progression free survival (PFS).

Results: A total of 40 pts were included into part 1, 21 pts were randomized to Nivo+SOX and 19 to Nivo+CapeOX. The median age was 62.5 years, 27 pts (67.5%) were male, 20 pts (50.0%) had ECOG PS 1. Median duration of treatment was 7.03 months (range 0.1-9.9) as of 24 Feb 2017. Both treatments were well tolerated. Grade 3-4 treatment-related adverse events (AEs) were reported 23 pts (57.5%). No Nivo-related AEs leading to discontinuation were reported. Overall response rate was 68.4% (26/38, CR10, PR16) and disease control rate was 86.8%. Median PFS was not reached. 18 pts (46.2%) remain on treatment at the time of the data cut off. There were no significant differences in activity and safety between the 2 treatments.

Conclusions: Nivo+SOX/CapeOX were feasible with promising activity as the 1st-line chemotherapy in pts with previously untreated unresectable advanced or recurrent G/GEJ cancer. Part 2 of the study is ongoing.

Clinical trial identification: NCT02746796

Legal entity responsible for the study: Ono Pharmaceutical Co., ltd.

Funding: Ono Pharmaceutical Co., ltd., Bristol-Myers Squibb

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672P A multicentre, phase II study with cabazitaxel in previously treated patients with advanced or metastatic adenocarcinoma of the oesophagogastric junction and stomach (CABAGAST)

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Background: This is a single-arm study (NCT01956149) to determine prolonged (> =4 months) disease control rate with cabazitaxel administered in second- (or later) setting for patients with advanced or metastatic adenocarcinoma of the esophagogastric junction (EGJ) and stomach.

Methods: 65 patients with advanced EGJ and stomach cancer were treated with 20mg/m2 Cabazitaxel every 3 weeks for a maximum of 6 cycles. Main objective of the study was a prolonged Disease Control Rate (pDCR: CR, PR or SD lasting at least 4 months). Secondary Outcome Measures were overall survival (OS), progression-free survival (PFS), response rate by subgroup (with vs without previous treatment with a taxane) and toxicity. Patients were assessed for tumor response every 6 weeks during therapy and during follow-up (up to 12 months).

Results: 65 patients (median age: 63, range 31-86 years) were assigned to treatment. Median no. of prior therapies was 2. 80% had received prior taxane therapy. Patients received a median of 2 cycles of cabazitaxel. Efficacy results are for the per protocol (PP) population. pDCR was 12.7%, (95%CI: 5.3%- 24.5%). pDCR was 20.0% in 2nd line patients (95%CI: 6.8%-40.7%) and 30.0% (95%CI: 6.7%-65.2%) in all lines in patients without prior taxane use. Response rate was 5.5% (95%CI: 1.1%-15.1%) in total PP and 20.0% in the population without prior taxane use. Median OS was 4.6 months (7.4 months without prior taxane vs 3.8 months with prior taxane). Median PFS was 1.38 months (95%CI: 1.28- 1.87) with and 2.01 months (95%CI: 0.20- 4.67) without prior taxane use. Most common grade 3/4 toxicities were neutropenia in 13% of the patients, pain (12%), leucopenia (10%), anemia (10%), fatigue (10%) and nausea (10%).

Conclusions: Cabazitaxel is active in heavily pretreated patients with metastatic and advanced esophagogastric junction and gastric adenocarcinoma. Toxicity is moderate. Patients without prior taxane use derived more benefit from Cabazitaxel.

Clinical trial identification: NCT01956149

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

Funding: Sanofi

Disclosure: All authors have declared no conflicts of interest.

673P Comparison of cytotoxic backbones for first line trastuzumab-containing regimens in HER2-positive advanced esophagogastric cancer: A meta-analysis

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Background: According to the ToGA study, trastuzumab plus cisplatin and capecitabine/5-fluorouracil (5-FU) is standard first-line treatment for HER2+ advanced esophagogastric cancer. However, optimality of this cytotoxic backbone is questioned. We examined the relative efficacy and safety of alternative trastuzumab-based cytotoxic backbone regimens compared to standard ToGA using meta-analysis.

Methods: Medline, EMBASE, CENTRAL and ASCO and ESMO were searched up to March 2017 for studies investigating alternative first-line trastuzumab-based regimens for patients with HER2+ esophagogastric cancer, with protein expression IHC3+ or IHC2+ and gene amplification by in situ hybridisation (ISH+). We compared overall survival (OS) of alternative trastuzumab-based regimens to trastuzumab plus cisplatin and capecitabine/5-FU of the ToGA trial IHC3+ or IHC2+/ISH+ subgroup. Hazard ratios (HR) and 95% confidence intervals (95%CI) were calculated by extraction of published Kaplan-Meier curves. Incidence counts and toxicity sample sizes were extracted for grade 1-2 and grade 3-4 adverse events and compared using single arm proportion meta-analysis.

Results: We included 15 studies (557 patients). For doublet backbone regimens, OS was significantly longer with trastuzumab plus oxaliplatin and capecitabine/5-FU compared to the ToGA regimen (median OS 20.7 vs 16.0 months, HR 0.75, 95%CI 0.59-0.99) and showed a more convenient toxicity profile. The doublet backbone trastuzumab plus cisplatin and S-1 showed no significant difference in OS compared to the ToGA regimen, but had a different toxicity profile, including less grade 1-2 hand-foot syndrome. Trastuzumab plus singlet backbone cisplatin or capecitabine had a significantly worse survival compared to the ToGA regimen and were more toxic. Trastuzumab with triplet cytotoxic backbones or with bevacizumab and doublet cytotoxic backbone had no survival benefit and were generally more toxic compared to ToGA.

Conclusions: Trastuzumab plus a doublet cytotoxic backbone containing oxaliplatin is preferable compared to the conventional ToGA regimen with cisplatin. S-1 can substitute capecitabine or 5-FU when specific toxicities are encountered.

Legal entity responsible for the study: N/A

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674P Nivolumab (NIVO) in patients (pts) with advanced (adv) chemotherapy-refractory (CT-Rx) esophagogastric (EG) cancer according to microsatellite instability (MSI) status: checkmate 032

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Background: NIVO improved OS vs placebo in Asian pts with gastric/gastroesophageal junction cancer in the phase 3 ATTRACTION-2 study (Kang YK, et al. ASCO GI 2017 [abstract 2]). In CheckMate 032, NIVO ± ipilimumab (IPI) demonstrated ORRs of 14% (NIVO monotherapy) and 26% (NIVO 1 mg/kg + IPI 3 mg/kg) in CT-Rx EG cancer (NCT01928394; Janjigian YY, et al. ASCO 2017 [abstract 4014]). The Cancer Genome Atlas identified MSI-high (MSI-H) EG tumors as having therapeutic targets that may make them responsive to immune checkpoint inhibitors. This exploratory analysis evaluated ORR and OS by MSI status in pts with EG cancer treated with NIVO monotherapy in CheckMate 032.

Methods: Pts with adv CT-Rx EG (including gastric, esophageal, and gastroesophageal junction) cancer were treated with NIVO 3 mg/kg every 2 weeks (n = 59). MSI status was centrally assessed using a PCR-based assay. Best objective response (BOR), ORR, and DCR (BOR of CR, PR, or SD) per investigator (INV) were assessed per RECIST v1.1.

Results: MSI status was determined in 25 pts; 7 (28%) were MSI-H, and 18 (72%) were non–MSI-H. ORR per INV was 29% in MSI-H pts, 11% in non–MSI-H pts, and 9% in pts with unknown MSI (MSI-U). DCR was 71%, 28%, and 26%, respectively. Of the 7 responders, 3 were PD-L1^{+} ($\geq$1% tumor expression; 1 per MSI category), 3 were PD-L1^{-} (MSI-U, n = 2; non–MSI-H, n = 1), and 1 was not evaluable for PD-L1 assessment (MSI-H). BOR is shown in the Table. Median OS (95% CI) was 14.75 mo (1.51, NA) in MSI-H pts, 6.49 mo (2.96, 12.42) in non–MSI-H pts, and 5.03 mo (2.76, 16.16) in MSI-U pts. Safety for the full EG cohort was previously reported (Janjigian YY, et al. ASCO 2016 [abstract 4010]).

Table: 674P ORR and BOR per INV according to MSI status

	MSI-H n = 7	Non–MSI-H n = 18	MSI-U n = 34
ORR, n (%) [95% CI]	2 (29) [4, 71]	2 (11) [1, 35]	3 (9) [2, 24]
BOR, n (%)			
CR	1 (14)	0	0
PR	1 (14)	2 (11)	3 (9)
SD	3 (43)	3 (17)	6 (18)
PD	2 (29)	11 (61)	21 (62)
Not evaluable	0	2 (11)	4 (12)

Conclusions: In this subgroup analysis, 7 pts (28%) were MSI-H, representing a biologically unique subset of EG tumors. NIVO monotherapy led to survival benefit and responses in both MSI-H and non–MSI-H pts.

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Legal entity responsible for the study: Bristol-Myers Squibb

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675P Involvement of the immunoregulator MZB1 in progression of gastric cancer

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Background: The initiation and progression of gastric cancer are associated with inappropriate immune responses caused by chronic inflammation of the gastric mucosa.

Methods: To identify immunoregulatory molecules involved in gastric cancer progression, transcriptome analysis was conducted using tissues from patients with metastatic gastric cancer. Gastric cancer cells lines and 200 pairs (cancerous and non-cancerous) of gastric tissues from patients with gastric cancer were analyzed for gene expression, amplification, DNA hypermethylation and functions of the candidate molecule.

Results: The transcriptome analysis revealed that marginal zone B and B1 cell specific protein (MZB1) was expressed at significantly decreased levels in primary gastric cancer tissues when compared with the corresponding normal gastric mucosae. PCR array analysis exploring genes expressed cooperatively with MZB1 revealed that differential expression of MZB1 mRNA in gastric cancer cell lines correlated positively with the levels of the mRNAs encoding estrogen receptor 1 and desumoylating isopeptidase 1. Hypermethylation of the MZB1 promoter was frequent in cell lines with decreased levels of MZB1 mRNA. siRNA-mediated knockdown of MZB1 significantly increased proliferation, invasion and migration of gastric cancer cell lines. Low MZB1 expression was an independent prognostic factor for recurrence after curative gastrectomy and was associated significantly with increased haematogenous recurrence.

Conclusions: The immunoregulator MZB1 acts as a suppressor and serves as a predictor for recurrence after curative resection in gastric cancer.

Legal entity responsible for the study: Mitsuro Kanda

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Disclosure: All authors have declared no conflicts of interest.

676P PD-L1 immunohistochemistry (IHC) by three different assays and molecular profiling in tissue microarray (TMA) of gastric cancer

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Background: Recent genomic and molecular characterization of gastric adenocarcinoma (GAC), such as Cancer Genome Atlas (TCGA), have shed light on the PD-L1 positivity and four different subtypes. Several PD-L1 IHC assays of scoring-criteria are developed in parallel. This study aimed to evaluate PD-L1 staining patterns and molecular profiling by TMA in GAC.

Methods: In total, 331 consecutive patients (pts) with GAC underwent curative surgery at Aichi Cancer Center Hospital between Jan 2009 and Dec 2010. Pts with no systemic chemotherapy before surgery and sufficient tumor content on the formalin-fixed and paraffin-embedded (FFPE) slides were eligible. EBV-encoded RNA in situ hybridization, IHC for deficient mismatch repair proteins (dMMR, MLH1/MSH2/MSH6/PMS2), HER2 and PD-L1 (22C3, 28-8, E1L3), and HER2 DISH were evaluated in TMA. Four cores of tumor tissue were punched out from individual FFPE tumor blocks and arrayed in a new TMA block. PD-L1 tumor positivity was categorized to $\geq$1%/$\geq$25%/$\geq$50% tumor cell membrane staining. Disease free survival (DFS) and overall survival (OS) were estimated by the Kaplan-Meier method.

Results: Among the cases, 226 pts were included in this study, excluding pts with prior chemotherapy (n = 26) and insufficient tumor samples (n = 79). Patient characteristics were as follows: male/female, 162/64; pStage (AJCC 7th ed.) I/II/III/IV, 100/39/58/29; EBV +/-, 13/213; proficient MMR/dMMR, 197/29, HER2 +/-, 24/202, and PD-L1 $\geq$1%/$\geq$25%/$\geq$50% (22C3 vs. 28-8 vs. E1L3), 11/4/2 vs. 7/6/6 vs. 12/10/8. Among 22C3, 28-8, and E1L3 assays, 94–97% of the pairs were concordant. PD-L1 positivity by all three assays was associated with EBV + ($p < 0.05$), whereas only 28-8 staining positivity was correlated with dMMR ($p = 0.04$). EBV+, dMMR, and HER2+ were mutual except three pts who had both dMMR and HER2+. There was no significant difference in DFS and OS among EBV, MMR, HER2 and PD-L1 status.

Conclusions: The three tested PD-L1 assays did not show comparable staining patterns in all cases. Studies that correlate not only PD-L1 staining patterns but also EBV+/dMMR/HER2+ and response to immunotherapy are required to evaluate.

Table: 676P

	EBV+ N = 13	EBV− N = 213	*P*	pMMR N = 197	dMMR N = 29	*P*	HER2+ N = 24	HER2− N = 202	*P*
E1L3 + −3 10	9 204	0.02	8 191	4 25	0.060	24	12 190	0.62	
28-8 + −3 10	4 209	<0.01	4 193	3 26	0.040	24	7 195	1.00	
22C3+ −3 10	8 205	0.02	8 188	3 26	0.162	22	9 193	0.32	

Legal entity responsible for the study: None

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Disclosure: All authors have declared no conflicts of interest.

677P Treatment of advanced gastric cancer based on Lauren's histological: Real-world data from the AGAMEMON National Cancer Registry

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Background: The choice of first-line chemotherapy in advanced HER2-negative gastric cancer (AGC) is based on the center's preferences and adverse effects profile. There is neither a standard accepted regimen nor predictive factors for drug response in clinical practice other than HER2 status. The objective is to evaluate whether Lauren's classification influences the efficacy of different chemotherapies and the survival of patients.

Methods: The data come from a national registry of AGC in which 31 Spanish centers participate. Eligibility criteria include the diagnosis of a stomach or gastroesophageal junction adenocarcinoma, HER2 negativity, and the use of two or three drug chemotherapy combinations. We used Cox proportional hazards (PH) regression with treatment-by-histology interaction tests to estimate the therapeutic effects.

Results: The registry contains 1215 HER2-negative tumors that could be analyzed for survival endpoints and 675 evaluable for overall response rate (ORR). Overall, the study failed to confirm a decrease in the ORR in the presence of diffuse component (Mantel-Haenszel, common odds ratio of 0.744 (CI 95%, 0.538-1.030), P = 0.088, nor heterogeneity of response according to histology. However, in the intestinal type, docetaxel-based or anthracycline-based regimens were more active than oxaliplatin-fluoropyrimidine regimens (ORR 62% and 60% vs. 45%, P < 0.05) and the latter had a higher ORR (within this histological group) compared to cisplatin-fluoropyrimidine (45% vs 28%, P = 0.0292). The diffuse type showed an increase in mortality with a hazard ratio HR of 1.231 (CI 95%, 1,070-1,417), P = 0.0036. In subgroup analyses, docetaxel-based regimens were associated with increased survival only in the subgroup with intestinal tumors: HR 0.74 (95% CI, 0.55-0.99), P = 0.037. Subgroup analyses for progression-free survival showed consistent effects in each subgroup.

Conclusions: In this registry, tumor subtypes based on Lauren's classification predicted survival, and responded differently to chemotherapy. Future clinical trials should stratify estimates of effects based on histology.

Legal entity responsible for the study: The investigators

Funding: None

Disclosure: All authors have declared no conflicts of interest.

678P Comparison of oxaliplatin-related spleen enlargement in patient with gastric cancer who received S-1 versus capecitabine as a combination partner of oxaliplatin

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Background: Oxaliplatin (OX)-based chemotherapy is known to cause hepatic sinusoidal injury, resulting portal hypertension with splenomegaly (SM). We compared this OX-induced hepatopathy, SM, and their clinical significance according to combined oral fluoropyrimidines, S-1 vs. capecitabine (X) in gastric cancer (GC).

Methods: We analyzed pts from two prospective trials for GC, adjuvant XELOX (X 1000 mg/m^2 bid on D1-14 + OX 130 mg/m^2 on D1 q3w, 8 cycles; n = 52) and palliative SOX (S-1 40 mg/m^2 bid on D1-14 + OX 130 mg/m^2 on D1 q3w, continuous [SOX-c, n = 52] vs. intermittent [SOX-i, discontinuing after 6th and restarting on progression, n = 53]) Spleen volume (vol) was retrospectively measured by *Rapidia software*.

Results: Baseline sex, age, ECOG PS, BSA, spleen vol, levels of platelet (plt)/liver enzyme/bilirubin (bil) and OX cumulative dose during 8 cycles did not differ in XELOX and SOX-c. After 8 cycles, the SOX-c had more SM, hepatic enhancing heterogeneity, hyper-bil, and thrombocytopenia than the XELOX (Table). The SOX-c was a risk factor for developing SM (adjusted odds ratio, 4.7; 95% CI, 2.0-10.8; p<.001) When tracking serial spleen vol and plt at baseline, 2nd, 4th and 6th cycles in SOX-c and SOX-i, spleen vol significantly increased over time (mean, 160, 182, 216, 247 cm^3; p<.001), whereas plt were decreased (mean, 290, 168, 132, 116 x10^3/uL; p<.001). In SOX-i group, spleen vol decreased at 6th cycles, 6, 12, 18 and 24w after stopping SOX (mean, 194, 181, 167, 158, 150 cm^3; p=.016).

Conclusions: S-1 seems to enhance OX-induced hepatic sinusoidal injuries than capecitabine in pts with GC with clinical significance of higher incidences of splenomegaly, thrombocytopenia, and hyperbilirubinemia.

Legal entity responsible for the study: Sook Ryun Park

Funding: None

Disclosure: All authors have declared no conflicts of interest.

679P Safety and efficacy of S-1 treatment in elderly patients with advanced or recurrent gastric cancer: A subgroup analysis from the phase III JFMC36-0701 trial

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Background: Chemotherapy is often considered for elderly patients with advanced or recurrent gastric cancer. However, there are no prospective trials evaluating outcomes

Table: 678P

		After 8 cycles, n (%)					
		XELOX	SOX-c	*p*	No SM	SM	*p*
Spleen vol	Mean <1.5 times ≥1.5 times (SM)	197.5 38 (73) 14 (27)	279.7 19 (36) 33 (63)	<.001 <.001			
Hepatic enhancing heterogeneity	Gr 0-1 Gr 2-3	45 (86) 7 (13)	33 (63) 19 (36)	.007	46 (81) 11 (19)	32 (68) 15 (32)	.139
Plt	Mean >150k ≤150k	148k 20 (38) 32 (61)	115k 11 (21) 41 (79)	.003 .054	157k 27 (47) 30 (53)	100k 4 (8) 43 (91)	<.001 <.001
Bil	Mean ≤ 1.2 > 1.2	0.8 44 (85) 8 (15)	1.1 33 (63) 19 (36)	.026 .014	0.8 49 (86) 8 (14)	1.2 28 (60) 19 (40)	<.001 .002

of chemotherapy in elderly patients with gastric cancer. Safety and efficacy of S-1 treatment in elderly versus younger patients were evaluated in the phase III JFMC36-0701 trial.

Methods: Between February 2007 and June 2010, 309 patients with advanced or recurrent gastric cancer were randomly assigned to S-1alone or S-1plus lentinan treatment; 134 patients (43.4%) enrolled were ≥75 years of age (range, 75-94) and 175 (56.6%) were <75 years of age (range, 30-74). S-1 was given orally in the dose of 40 mg/m2 twice daily for the first 4 weeks of a 6-week cycle. Lentinan was given as an intravenous infusion of 2 mg/body every week. Overall survival (OS), overall response rate (ORR) and safety were compared between patients aged ≥75 and <75 years.

Results: Patient characteristics were comparable between the two cohorts. OS was 12.8 (95% CI 10.7-14.9) and 11.5 (95% CI 9.5-13.4) months for patients aged ≥75 and <75 years, respectively with no statistical difference. The ORR was evaluable in the 190 patients with measurable disease at baseline. The ORR was 23.4% and 18.6% in patients aged ≥75 and <75 years, respectively. Disease control rates were also similar: 44.2% versus 48.7% for elderly versus younger patients. Rates of neutropenia (≥grade3) were comparable for elderly and younger patients (12.7% versus 10.4%), and the incidences of non-hematologic adverse events (≥grade3) such as anorexia, vomiting and fatigue were also similar in both elderly and younger patients (12.7% versus 10.4%, 0% versus 1.8% and 7.9% versus 4.9%, respectively).

Conclusions: This subgroup analysis suggests that elderly patients with advanced or recurrent gastric cancer derive similar benefit from S-1 treatment to younger patients, with acceptable toxicity.

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Legal entity responsible for the study: Japanese Foundation for Multidisciplinary Treatment of Cancer

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680P Phase II study of modified docetaxel, cisplatin and S-1 (mDCS) combination chemotherapy in patients with unresectable metastatic gastric cancer

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Background: We have previously conducted phase II studies to evaluate the effect of adding docetaxel to base treatment with S-1 plus cisplatin (DCS) to further improve the therapeutic response; both a very high response rate (87.1%) and a promising median survival time (687 days) in patients with unresectable advanced gastric cancer were noted (Y. Sato et al. Cancer Chemother Pharmacol. 2009); however, it also showed a high incidence of grade 3/4 toxicity. With the aim of reducing toxicities, we conducted a phase II study of modified DCS (mDCS), using a reduced dose of docetaxel, and evaluated the clinical efficacy and adverse events of this regimen.

Methods: Patients with unresectable gastric cancer received chemotherapy with S-1 (40 mg/m^2 b.i.d) on days 1–14, and docetaxel (50 mg/m^2) plus cisplatin (60 mg/m^2) on day 8 every 3 weeks. The primary endpoint was the response rate (RR). Overall (OS) and progression-free survival (PFS), and toxicities were also evaluated.

Results: Forty-nine patients were enrolled from November 2011 to April 2014, and 47 were eligible. The overall RR was 78.8%, including two cases of a complete response (4.3%), and 35 cases of a partial response (74.5%). Ten cases had stable disease (21.3%) but none showed progressive disease. Of the 47 cases, 16 cases (34.0%) underwent curative conversion surgery. The median PFS was 350 days (95% CI; 238–406 days) and median OS was 561 days (95% CI; 401–783 days). Grade 3/4 neutropenia developed in 76.6%, and febrile neutropenia in 31.9%, of patients. Non-hematological grade 3/4 adverse events were anorexia (23.4%), nausea (4.3%), and diarrhea (8.5%).

Conclusions: mDCS therapy showed high clinical efficacy and fewer toxicities, but careful management of these is still essential.

Clinical trial identification: UMIN000002361

Legal entity responsible for the study: Tokushima-Hokkaido cancer therapy clinical trial group, Tetsuji Takayama

Funding: None

Disclosure: All authors have declared no conflicts of interest.

681P Clinical impact of programmed death ligand-1 and -2 expression after platinum based chemotherapy in metastatic gastric cancer

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Background: The effect of chemotherapy on programmed death ligand-1 (PD-L1) and PD-L2 expression is not well known. Therefore we aimed to investigate the effect of chemotherapy to PD-L1/2 expression in metastatic gastric cancer (mGC).

Methods: We evaluated the PD-L1 and 2 expression of 63 patients with paired tumor tissue before and after 3 to 4 cycles of palliative first line platinum-based chemotherapy. PD-L1/2 expression was detected by immunohistochemistry(IHC) method in paired tumor specimens.

Results: There were no significant differences in PD-L1 and PD-L2 expression across various clinicopathological parameters. The detection of PD-L1 on tumor cells decreased from 58% to 38% after chemotherapy ($p = 0.028$), but not with PD-L2 (from 43% to 36%). Among patients with objective response (CR and PR), PD-L1 expression decreased with statistical significance ($p = 0.033$), but not among patients with SD and PD ($p = 0.275$). In univariate and multivariate analysis, patients with positive PD-L1 at the pre-chemotherapy showed better progression free survival (PFS, hazard ratio [HR]=0.42, $p = 0.014$). In contrary, after chemotherapy, patients with positive PD-L1 showed decreased PFS (HR = 1.97, $p = 0.023$). And pre-chemotherapy PD-L1 statuses didn't have any correlation with OS difference, however, post-chemotherapy negative PD-L1 prolonged OS (HR = 1.92, $p = 0.047$). PD-L2 statuses had no difference of PFS and OS before and after chemotherapy. Univariate and Multivariate analysis showed that negative to positive change and positive to negative change of PD-L1 expression was associated with poorer PFS (HR = 0.030, $p = 0.03$) and better PFS (HR = 0.02, $p = 0.024$), respectively.

Conclusions: Our data suggests that chemotherapy may have an effect on the status of PD-L1/L2 expression. PD-L1/L2 expression may change during chemotherapy, so we suggest monitoring the pattern of change through serial tumor samples to reflect the correct status of PD-L1 expression.

Legal entity responsible for the study: In-Ho Kim

Funding: None

Disclosure: All authors have declared no conflicts of interest.

682P Clinical practice observation of trastuzumab (TRA) in patients (pts) with HER2-positive metastatic adenocarcinoma of the stomach (mGC) or the gastro-oesophageal junction (GEJ): Final analysis from the German non-interventional study HerMES

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Background: HER2-pos metastatic cancer of GEJ or stomach are indications with a high medical need. TRA plus standard chemotherapy (CT) has been approved as 1L therapy in HER2-pos mGC or mGEJ-C pts according to ToGA-study. HerMES (NCT01220934) was designed to collect data on clinical routine practice in 171 specialist centers in Germany.

Methods: Between January 2010 and July 2016, 434 pts were identified. 364 pts matched criteria for TRA-therapy and were treated accordingly (population of the present analysis). Another 39 pts did not match criteria for HER2-positivity with TRA-therapy and will be evaluated separately. Main parameters of interest were overall response rate (ORR), progression free survival (PFS), safety and overall survival (OS). QoL and patient reported outcomes will be presented later.

Results: Mean age was 65 years, 75% were male, and 51% had mGEJ-C. TRA was given at an average dose of 5.73 mg/kg. Mean treatment duration for TRA was 7 months (mos) and 61 pts (17%) received TRA-therapy for more than 1 year. CT regimen frequently used were cisplatin/5-FU (21%), oxaliplatin/5-FU/docetaxel (10%), and cisplatin/capecitabine (8%). ORR was 43% [95%CI 0.38;0.49], median PFS was 7 mos [6.3;7.6], and median OS was 10 mos [8.8;11.1]. Most frequent related AEs (reported in > 5% of pts) were diarrhea in 29 (8%), nausea in 24 (6.6%) and fatigue in 22 cases (6%). TRA-rel cardiac AEs occurred in 21 pts (6%).

Conclusions: To our knowledge this is the largest prospective observational trial on TRA in the daily clinical routine care of metastatic GC/GEJ-C. Chemotherapy backbones were diverse. The outcome was similar to ToGA, taking into account the unselected patient population.

Clinical trial identification: NCT01220934

Legal entity responsible for the study: Roche Pharma AG

Funding: Roche Pharma AG

Disclosure: S-E. Al-Batran: Membership on advisory board or board of directors: Lilly Pharma, BMS, Roche, Astellas C. Maintz: Membership on advisory board or board of directors: Roche, Shire P. Thuss-Patience: Membership on advisory board or board of directors: Roche, Lilly, MSD, BMS, Nordic Corporate-sponsored research: Novartis V. Gaillard: Other substantive relationship such as employment with a pharmaceutical company: Roche Pharma AG (Employment) All other authors have declared no conflicts of interest.

683P Intratumoral PD-L1 expression is associated with worse survival of patients with Epstein-Barr virus-associated gastric cancer

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Background: This study investigated the clinical relevance and prognostic impact of the overall expression of programmed cell death protein ligand-1 (PD-L1) and programmed cell death protein ligand-2 (PD-L2), in patients with Epstein-Barr virus-associated gastric cancer (EBVaGC).

Methods: After reviewing 1318 consecutive cases of surgically resected or endoscopic submucosal dissected gastric cancers, the expression status of PD-L1 and PD-L2 in 120 patients with EBVaGC identified by EBV-encoded RNA *in situ* hybridization was retrospectively analyzed using immunohistochemistry (IHC). For each IHC marker, positivity was separately in intraepithelial tumor cells (iTu-) and immune cells in the tumor stroma area (str-).

Results: Among 116 eligible patients, 57 (49.1%) and 66 patients (56.9%) were determined as iTu-PD-L1-positive and str-PD-L1-positive, respectively, while 23 (21.6%) and 45 patients (38.8%) were determined as iTu-PD-L2-positive and str-PD-L2-positive, respectively. iTu-PD-L1-positivity was found to be significantly associated with lymph node (LN) metastasis (p=0.012) and a poor disease-free survival (DFS)(P=0.032), yet not overall survival (p=0.482). Meanwhile, str-PD-L1-positivity was correlated with the density of iTu- and str-tumor-infiltrating lymphocytes (TILs)(P=0.003, P=0.004, respectively), yet not the patient outcomes. In contrast, str-PD-L2-positivity was related to a lower T category (P=0.003), absence of LN metastasis (P=0.032) and perineural invasion (P=0.028), and iTu- and str-TILs (P<0.001, P<0.001, respectively). iTu- and str-PD-L2-positivity showed a trend towards an improved DFS, although not significant (P=0.060, P=0.073, respectively). In a multivariate analysis, iTu-PD-L1-positivity was independently associated with a poor DFS (P=0.006, Hazard ratio=12.085).

Conclusions: iTu-PD-L1 expression can be used to predict a poor outcome in patients with EBVaGC, and can represent a rational approach for PD-1/PD-L pathway-targeted immunotherapy.

Legal entity responsible for the study: N/A

Funding: None

Disclosure: All authors have declared no conflicts of interest.

684P Targeting c-met and DNA double-strand break (DSB) repair pathways for BRCA-mutated gastric carcinomas

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Background: In the present study, we underline the importance of combining c-Met Inhibitor (Inh.) and DSB repair Inhibitor (PARP Inh.) with the goal of accomplishing a synergistic therapeutic strategy in BRCA-mutated gastric carcinomas.

Methods: Firstly, to verify whether c-Met affects tumor response to PARP Inh., AGS (low c-Met expression) and Hs746T (high c-Met expression) cell lines, were subjected to knockdown c-Met expression, in the presence of PARP Inh. (NU1025). Subsequently, we examined the correlation between BRCA1/2 and c-Met. We knocked down BRCA1/2 expression in AGS and Hs746T cells and treated them with PARP Inh. Next, we examined the effects of combining c-Met Inh. (SU11274) and PARP Inh. (NU1025), measured by MTT, clonogenic cell survival and Annexin, assays. We also evaluated the effect of combining PARP Inh. and c-Met Inh. in AGS/Hs746T xenograft tumor models. AGS/Hs746T -pcDNA3 and AGS/Hs746T -si*BRCA* cells were injected into SCID mice. Tumor sizes were measured every 3 days. DNA damage was assessed by γ-H2AX staining.

Results: Silence of Met expression promoted Hs746T cells more sensitive to PARP Inh. to similar levels as the AGS cells, as indicated by decreased cell viability. Silence of BRCA1/2 expression sensitized only AGS cells, signifying that increased expression of c-Met renders cells resistant to PARP Inh. in the context of inactivating BRCA1/2. Combining c-Met Inh. and PARP Inh. suppressed cell growth and clonogenicity and enhanced apoptosis in both AGS and Hs746T cells. The dual inhibition was demonstrated to be even more successful when cells were knockdown for BRCA1/2. Also, co-inhibition treatment substantially reduced tumor growth to AGS/Hs746T -pcDNA3 and more even effectively to AGS/Hs746T –si*BRCA1/2* xenograft models, compared to either Inh. alone. DNA damage was higher in AGS/Hs746T –si*BRCA1/2* compare to AGS/Hs746T -pcDNA3 xenograft models.

Conclusions: BRCA deficiency renders gastric tumor cells sensitive to PARP inhibition. In addition, treatment with c-Met Inh. enhanced Hs746T sensitivity to the PARP Inh. Our data demonstrate that dual Met/PARP inhibition is synergistic providing an effective therapeutic strategy in BRCA-mutated gastric carcinomas.

Legal entity responsible for the study: M.V. Karamouzis

Funding: None

Disclosure: All authors have declared no conflicts of interest.

685P Clinical efficacy observation for endostar combined with chemotherapy treating gastric cancer peritoneal carcinomatosis

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Background: The peritoneal carcinomatosis of gastric cancer is a current therapeutic difficulty and the related clinical data are still limited so far. In this study, we evaluated efficacy and safety of the recombinant human endostatin (Endostar) characterized by broad-spectrum anti-angiogenesis combined with chemotherapy on gastric cancer peritoneal carcinomatosis.

Methods: From Jan. 2014 to Dec. 2016, 33 advanced stage gastric cancer patients associated with peritoneal carcinomatosis were enrolled. Their pathological information, imaging as well as therapy information were retrospectively analyzed. Twenty-one patients only received systemic chemotherapy as control group, and twelve patients received Endostar combined with chemotherapy as combination therapy group. All the 33 patients were evaluated on phase-efficacy and followed-up to record survival time. The tumor time to progression (TTP), overall survival (OS), Objective Response Rate (ORR), disease control rate (DCR) and therapy-related adverse reactions were evaluated to confirm effect of Endostar therapy.

Results: All the patients were evaluable. The evaluation on efficacy indicated that Endostar combined with chemotherapy increased ORR (41.6% vs. 23.81%) and DCR (83.3% vs. 61.91%) compared with control group, although there was no statistical difference between them. The survival analysis indicated that Endostar combined with chemotherapy effectively extended time to disease progression (4.60 ± 0.32 months vs. 3.50 ± 0.34 months, P = 0.03), and the median OS (15.80 ± 3.4 months vs. 9.80 ± 0.7 months, P = 0.01) compared with single chemotherapy. Furthermore, the evaluation on adverse reactions indicated that combination therapy did not have more adverse reactions.

Conclusions: The recombinant endostatin with broad-spectrum anti-angiogenesis could effectively control the development of peritoneal carcinomatosis disease and extend survival with high safety and tolerance. However, further prospective study needs to be performed to confirm the clinical application value.

Clinical trial identification: This retrospective study was approved by hospital ethical committee and all informed consent were obtained.

Legal entity responsible for the study: This study was approved by hospital ethical committee and all informed consent were obtained.

Funding: None

Disclosure: All authors have declared no conflicts of interest.

686P Modified epirubicin and oxaliplatin plus capecitabine (EOX) Regimen as second-line therapy after failure of modified docetaxel and cisplatin plus fuorouracil (DCF) regimen in advanced gastric cancer

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Background: In advanced gastric cancer, we aimed to evaluate the effectiveness of mEOX regimen as second line therapy after failure of mDCF regimen.

Methods: In between 2009 and 2016, the patients who were progressed after mDCF (docetaxel 60 mg/m^2 on day 1, cisplatin 60 mg/m^2 on day 1, Fluorouracil 600 mg/m^2/day for 5 days) and received mEOX (epirubicin 50 mg/m^2 on day 1, oxaliplatin 85 mg/m^2 day 1 and capecitabine twice-daily dose of 625 mg/m^2, p.o. for 2 weeks) every 3 weeks until progression or unacceptable toxicity, were retrospectively analyzed. Progression-free survival (PFS) was defined as the time interval from the day of progression on mDCF therapy to the date of disease progression or death after first cycle of EOX therapy.

Results: Total 129 patients were included to study population. Median age was 55 years (range= 27-78 years). Most of the patients were male (76%). Undifferentiated signet ring cell carcinoma was the most frequent histological subtype (72.1%). The most of the patients had eastern cooperative oncology group (ECOG) performance status 0-1 (72.9%). The most frequent regions of metastasis were; non-regional lymp nodes (55.8%), liver (45.7%), peritoneum (39.5%). Most of the patients (75.2%) had ≥ 2 regions of metastasis. The median number of chemotherapy courses was five (range= 2–

9). Forty-nine patient achieved a partial response and 33 patients showed stable disease, resulting in a ORR (overall response rate) of 38% and a DCR (disease control rate) of 63.6%. Most frequent grade 3-4 hematological and non-hematological toxicity was neutropenia (8.5%) and nausea/vomiting (5.4%). None of the patients had toxic death. The median PFS was 4.7 months (95% confidence interval [CI], 4.1–5.3), and OS was 7.4 months (95% CI, 6.3–8.5). In multivariate analysis age $\geq$ 60 years and ECOG performance status (0-1) were independent prognostic factors that affect PFS and OS.

Conclusions: In advanced gastric cancer patients, who were progressed after first line chemotherapy and having ECOG performance status 0-1, mEOX was well tolerated triple regimen with promising OS and PFS.

Legal entity responsible for the study: Ankara Numune Training and Research Hospital

Funding: None

Disclosure: All authors have declared no conflicts of interest.

687P Phase II clinical trial of second-line weekly paclitaxel plus trastuzumab for patients with HER2-positive metastatic gastric cancer

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Background: Combination therapy with fluorouracil, platinum, and trastuzumab (Tmab) has been established as the first-line chemotherapy for HER2-positive gastric cancer, but there is no established therapy in the second-line setting. This study aimed to evaluate the efficacy and safety of weekly paclitaxel plus Tmab as second-line chemotherapy for HER2-positive gastric cancer patients.

Methods: Eligible patients were $\geq$ 20 years old, histologically confirmed gastric adenocarcinoma with HER2-positive (IHC3+ or IHC2+ and FISH (or DISH)-positive), previously treated chemotherapy (not except pretreated-Tmab), ECOG PS of 0, 1 or 2, and adequate organ function. Eligible patients received weekly paclitaxel plus Tmab (paclitaxel: 80 mg/m^2 IV on day1, 8, 15, repeated every 4weeks, Tmab: 8mg/kg (1st time) IV on day1, after 2nd time, 6mg/kg IV, repeated every 3weeks). All therapy was administered until disease progression. The primary endpoint was response rate, the secondary endpoint were Progression-free survival (PFS), Overall survival (OS) and Toxicity.

Results: Twenty-eight patients were enrolled between 08/2011 and 03/2017. Patients characteristics were; median age, 69.5 years; male, 22(79%); ECOG-PS0/1/2, 5(18%)/17(61%)/6(21%); Tmab pretreated/untreated, 20(71%)/8(29%). The overall response rate was 22% with 6 partial responses, 8 stable diseases, 13 progression and 1 not evaluable yet. Median PFS was 4.6 months (95% CI: 2.2-7.0). Median OS was 9.6 months (95% CI: 2.3-16.9). Grade 3/4 toxicities included neutropenia in 36%, leukopenia in 21%, anemia in 11%, anorexia in 7%, febrile neutropenia in 7%, respectively. Tmab beyond progression (TBP) group (n = 20) did not differ from non-TBP group (n = 8) in PFS and OS (PFS; 5.0:2.8 (months), p = 0.369, OS; 12.4:6.1 (months), p = 0.363, log-rank test). And, in TBP group, therapeutic effect was associated with duration of PFS of 1st line Tmab combined chemotherapy ($\geq$ 6 months (n = 10): < 6 months (n = 10), PFS; 6.4:2.8 (months), p = 0.016, OS; Not reached:6.5 (months), p = 0.002, log-rank test).

Conclusions: Weekly paclitaxel plus trastuzumab appeared favorable and well tolerated as second-line chemotherapy for HER2-positive gastric cancer patients in this single arm study.

Legal entity responsible for the study: Toyama Prefectural Central Hospital

Funding: None

Disclosure: All authors have declared no conflicts of interest.

688P Beyond first line treatment for advanced esophagogastric adenocarcinoma (EGAC): A phase 1 dose escalation study of regorafenib (Reg) combined with paclitaxel (PTX) (REPEAT study)

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Background: Second line treatment with Ramucirumab inhibiting angiogenesis is effective as monotherapy and combined with PTX. Reg, a multikinase inhibitor of angiogenic, stromal, and oncogenic receptor tyrosine kinases is effective as monotherapy. Since survival remains poor new treatment strategies are needed. Therefore, we conducted a phase I dose escalation trial to determine the recommended dose for phase 2 testing (RP2D) of Reg with PTX.

Methods: Adult patients (pts) with metastatic EGAC who failed at least one prior treatment line, including a fluoropyrimidine and a platinum compound, received PTX 80 mg/m2 i.v. on day 1, 8 and 15 of a 28 day cycle, with Reg on day 1-21 in one of 3 dose levels (DL-1: 80, DL-2: 120, DL-3: 160 mg QD) in a standard 3 + 3 design. Tumor response was assessed every 2 cycles (RECIST v1.1). Pts were treated until progressive disease (PD) or unacceptable adverse events.

Results: We enrolled 14 pts (median age 63), 8 with esophageal and 6 with gastric cancer. Pts had received 1 (n = 7) or 2 (n = 7) prior lines of palliative chemotherapy and 13 pts were evaluable for dose limiting toxicity (DLT). No DLT occurred at DL-1, 1 DLT occurred at DL-2 (grade 3 hand-foot-syndrome), and 3 DLT's occurred in 2 pts at DL-3 (grade 3 mucositis, diarrhea and GGT elevation). RP2D of Reg was established at 120 mg. Other grade 3/4 toxicities were hypertension (29%), mucositis (21%) and non-febrile neutropenia (14%). Grade 1/2 toxicities included neuropathy (64%), hoarseness (57%), infections (50%), nausea/vomiting (43%), toxicodermia (43%), mucositis (36%), diarrhea (29%) and epistaxis (29%). Median follow up is 8.3 months with 2 pts still on treatment. Median number of cycles is 4. Reasons for stopping were PD (n = 9) or toxicity (n = 3). Best responses were PR (n = 1), SD (n = 12) and PD (n = 1). Median PFS is 4.2 and median OS 8.5 months.

Conclusions: RP2D of Reg combined with PTX is 120 mg QD. This combination is well tolerated and shows promising effects on survival in heavily pretreated patients. An expansion cohort to further study efficacy as well as the effect of Reg on PTX uptake and expression of downstream Reg targets in metastases is being accrued.

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Funding: Bayer

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689P Phase I dose escalation study with expansion cohort of the addition of nab-paclitaxel (nab-P) to capecitabine and oxaliplatin (CAPOX) as first line treatment of advanced esophagogastric adenocarcinoma (EGAC) (ACTION study)

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Background: The prognosis of advanced EGAC remains poor. Triplets containing taxanes show a survival benefit but at the cost of increased toxicity. Given the favorable toxicity profile of nab-P compared to conventional taxanes we conducted a phase 1 dose escalation study to find the maximum tolerated and recommended phase 2 dose (MTD/RP2D) of the addition of nab-P to CAPOX.

Methods: Patients (pts) with metastatic or non-resectable EGAC received oxaliplatin 65 mg/m2 day 1 and 8 and capecitabine 1000 mg/m2 bid day 1-14 in a 21 day cycle, with nab-P day 1 and 8 at 4 dose levels (DL1 60, DL2 80, DL3 100 and DL4 120 mg/m2, respectively) in a standard 3 + 3 design, followed by an expansion cohort of 20 pts. Tumor response was assessed every 3 cycles (RECIST 1.1). Pts were treated until progressive disease (PD), unacceptable toxicity or a maximum of 6 cycles after which capecitabine monotherapy was continued. Ox and nab-P were reintroduced if PD occurred after more than 3 months.

Results: We enrolled 26 pts (median age 63; 18 had esophageal cancer and 8 gastric cancer). Ten pts had received prior curative treatment. At DL1 and DL2 no dose limiting toxicity (DLT) occurred. At DL3 2 DLT's occurred (diarrhea and dehydration due to vomiting/diarrhea). MTD was established at 80 mg/m2 and chosen for evaluation in the expansion cohort. However, because of diarrhea grade 3 in 5/12 pts (42%) in the course of treatment the nab-P dose was reduced to 60 mg/m2. Grade 3/4 toxicity of all pts treated at this DL was nausea (18%), diarrhea, vomiting, anorexia and elevated GGT (all 9%). Notable grade 1/2 toxicities were neuropathy (82%), dysgeusia, diarrhea (both 64%), nausea (55%) and vomiting (45%). Best responses were PR (13 pts), SD (9 pts) and PD (2 pts). Median follow up is 9.1 months, 22 pts completed 6 cycles and 5

pts are still on treatment of whom 4 on capecitabine monotherapy. Median PFS is 8.0 months.

Conclusions: MTD of nab-P in combination with CAPOX is 80 mg/m2 and RP2D 60 mg/m2 in a 3-weekly schedule. Given the manageable toxicity at RP2D and promising efficacy, further evaluation of this regimen is warranted. Biomarker research is currently ongoing.

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690P KRAS status and HER2 targeted treatment in advanced gastric cancer

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Background: Trastuzumab targeted on HER2 has been shown to confer overall survival benefit adding to fluoropyrimidine (Fp) plus CDDP in HER2-positive advanced gastric cancer (AGC). HER2 is known to make the formation of heterodimer with EGFR, HER3 and HER4. HER2 containing heterodimer activates the common downstream of HER family such as MAPK pathway via RAS and PI3K pathway. *RAS* and *PIK3CA* mutations has been well known as predictive biomarkers for anti EGFR treatment in colorectal cancer and anti HER2 treatment in breast cancer. However it remains unclear that the implications for these status and HER2 targeted treatment in AGC. In this study we attempted to assess the relationship with the efficacy of trastuzumab including treatments and mutational status of molecules in HER family signaling pathway.

Methods: Out of over 500 AGC between March 2011 and November 2015 we chose 100 patients (pts) received Fp plus CDDP with trastuzumab as 1st-line, finally total 77 pts with sufficient specimen for DNA extraction were enrolled in this analysis. Multiplex genotyping of common downstream in HER family was performed on archival samples using Luminex Assay (MEBGEN and GENOSEARCH Mu-PACK, MBL) for *KRAS* and *NRAS* including exon 2, 3 and 4, *PIK3CA* and *BRAF*. *KRAS* amplification was measured by quantitative real-time reverse transcription- polymerase chain reaction. The relative level of *KRAS* mRNA was normalized by *HPRT-1* mRNA. We assessed the relationship between gene or mRNA status and clinical outcomes. Tumor response was re-assessed by the investigator retrospectively by RECIST1.1.

Results: *KRAS* mutation of exon2 was detected in only 6 patients of 77 pts (7.8%). No mutations were found in *NRAS*, *PIK3CA* and *BRAF* in this HER2 positive AGC series. *KARS* amplification was detected in 16 pts (20.1%) (cut-off > 3.0). An overall RR and the disease control rate (DCR) in *KRAS* wild type (WT) vs. mutant type (MT) were following, RR; 66.2% vs. 16.7%, DCR; 87.3% vs. 66.7%, respectively (CR2/0, PR 45/1, SD 15/3, PD 9/2). The median PFS and OS in *KRAS* WT vs. MT were as followed, 8.9 months (m) vs. 3.6 m and 20.8 m vs. 10.3 m, respectively. *KRAS* MT showed low response rate and extremely shorter PFS and OS compared with *KRAS* WT. On the other hands, *KRAS* amplification did not affect the clinical outcomes.

Conclusions: Our data suggested HER2-positive AGC harbored *KRAS* mutation at the low frequency. *KRAS* mutation was strong prognostic and might predict the lack of benefit as receiving HER2 targeted treatment. Further investigation was warranted to confirm the predictive value of *KRAS* status in HER2-positive AGC receiving trastuzumab to fluoropyrimidine plus CDDP.

Legal entity responsible for the study: Ethical Guidelines for Medical Research on Humans

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691P Inter-patient and intra-tumoral heterogeneity of oncogenic copy number alterations (CNAs) in gastric and gastroesophageal junction (GEJ) adenocarcinomas

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Background: Intra-tumoral heterogeneity is well recognized to be inherent in biomarker discovery for gastric cancer since the initial reporting of HER2 overexpression. The Cancer Genome Atlas (TCGA) has laid the groundwork for CNAs comprising the mutational landscape of gastric cancer. We aimed to investigate through a genomic single nucleotide polymorphism (SNP) array panel and fluorescence in-situ hybridization (FISH) inter-patient and intra-tumoral spatial heterogeneity of CNAs.

Methods: 41 gastric adenocarcinoma patient samples treated with upfront surgical resection were retrospectively identified from the City of Hope Biospecimen Repository. CNAs of 891 cancer-related genes at 50-100 Kb resolution and detection of 74 frequent somatic mutations in 9 genes of interest (*BRAF, KRAS, EGFR, IDH1, IDH2, PTEN, PIK3CA, NRAS, TP53*) were assayed using the Affymetrix OncoScan™ platform. Genome wide coverage outside of the 891 cancer genes were provided at 300 Kb resolution along with genome wide LOH provided at 3-10 Mb resolution. For samples with multiple CNAs detected, FISH was pursued to define down to a single-cell level the spatial distribution of CNAs.

Results: Detectable percentage (%) genomic changes ranged from 0.03 to 73.90%. Lauren intestinal subtype histology correlated strongly with higher % genomic changes compared to diffuse subtype histology ($p = 0.0012$). Tumors located in the GEJ/cardia/proximal stomach also correlated with higher % genomic changes compared to gastric body/antrum tumors ($p = 0.0028$). A variety of oncogenic CNAs were observed across patients including high copy gains in EGFR, JAK2, FGFR2, MET, VEGFA, KRAS, NRAS, and PIK3CA. One sample exhibited co-amplification of CD274 and PDCD1LG2 (encoding PD-L1 and PD-L2), in addition to concurrent amplification of ERBB2, JAK2, FGFR2, MET, KRAS, and PIK3CA. FISH images of the spatial distribution of CNAs will be presented.

Conclusions: The inherent spatial intra-tumoral heterogeneity of oncogenic CNAs with de novo disease presentation illustrates the challenges in gastric cancer therapy. Further study will offer insight into strategies on combinatorial and/or sequential targeted and immunotherapeutic approaches.

Legal entity responsible for the study: Joseph Chao

Funding: United States National Institutes of Health - National Cancer Institute

Disclosure: All authors have declared no conflicts of interest.

692P Identification of an RNF43 mutated gastric cancer patient population with potential sensitivity to porcupine inhibitor RXC004 and development of a complimentary ctDNA liquid biopsy assay for patient screening

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Background: RXC004 is a small molecule PORCN inhibitor, entering first-in-human trials in 2017. PORCN inhibition has been shown to have potential for the treatment of molecularly selected pancreatic and colorectal cancers, as well as the ability to synergise with anti-PD1 checkpoint inhibition. The aim of this study was to identify additional patient segments predicted to benefit from treatment with a PORCN inhibitor.

Methods: Mutation incidence for the WNT pathway gene RNF43 was analysed in 674 gastric cancer samples. RXC004 was profiled in gastric, pancreatic and biliary PDX models carrying the RNF43 mutations and growth inhibition was correlated with WNT pathway inhibition. To support the clinical trial a patient selection strategy, based on detection of RNF43 mutations from a liquid biopsy, using MassArray mass spectrometry technology is described.

Results: Bioinformatics data-mining of TCGA identified that the prevalence of RNF43 mutation in gastric cancer is 14-16%. A specific hot spot mutation (G659Vfs*41) has been identified, which accounts for ~70% of the RNF43 mutations. Profiling of RXC004 in RNF43 mouse models of gastric and pancreatic cancer shows the potential for monotherapy efficacy. In order to translate our findings to the clinic, we developed an assay suitable for detection of RNF43 mutations in circulating tumour DNA (ctDNA) from patient plasma. Multiplexed assays for RNF43 mutations, including the G659Vfs*41 hotspot, have been developed using MassArray technology. By converting to UltraSeek MassArray methodology we are targetting a sensitivity of 0.1% allelic frequency and specificity >99% in patient ctDNA.

Conclusions: RXC004 is entering first-in-human trials in 2017 with a modular phase I/IIa clinical protocol design which allows for phase IIa expansion arms in molecularly selected patient segments including gastric cancer. We demonstrate that there is an RNF43 mutated patient segment which may benefit from therapy with RXC004, and that these patients have the potential to be identified by a ctDNA screening approach.

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Legal entity responsible for the study: Redx Pharma Plc

Funding: Redx Pharma Plc

Disclosure: M. Bingham, I. Bhamra, R. Armer, S. Woodcock, A. Thomason, C. Phillips, H. McKeever: Employee of Redx Pharma Plc. B. Thompson: Employee of Redx Pharma Plc at the time of this work. B. Chaffey, L. Little: Employee of NewGene Ltd. G. Clack: Consultant for Redx Pharma Plc. All other authors have declared no conflicts of interest.

693P Prognostic effect of surgery of metastases in patients with advanced gastric cancer: Real-world data from the AGAMENON registry

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Background: The aim of this analysis was to evaluate the prognostic effect of surgery of metastases in patients from a national registry of advanced gastric cancer.

Methods: The effect of surgery of metastases was assessed by multivariable Cox proportional hazards regression adjusted by confounding factors. To avoid immortal time bias in variables that occur after the initial period of observation, surgery of metastases, primary tumor resection, and the assessment of tumor response by RECIST were considered as time-dependent variables. All P values are two-sided. Statistical analyses were performed using RStudio, including the survival package.

Results: The registry contains 1531 evaluable patients. Of these, 5.3% (n = 82) patients underwent surgery for metastases (liver metasectomies were performed in 23 patients, peritoneal surgeries in 39, a pulmonary metastasis excision in 1 patient, and 19 surgeries in other locations). The majority of the cases (53.6%) had a single metastatic location. The median overall survival in non-operated patients was 10.4 months (confidence interval [CI] 95%, 9.9-10.9) versus 19.8 months (CI 95%, 17.4-28.8) in patients with resection of metastases. In the multivariable Cox proportional hazards regression, the resection of metastases was associated with a reduction in mortality with a hazard ratio (HR) of 0.57 (95% CI, 0.43-0.76) (see Table 1). Table 1. Cox proportional hazards regression

Conclusions: In this registry of patients with advanced gastric tumors, surgery of metastases appears to confer a favorable survival benefit when performed on carefully selected patients.

Legal entity responsible for the study: The investigators

Funding: None

Disclosure: All authors have declared no conflicts of interest.

694P Comparison of HER2 related molecular expression and its significance for clinical outcomes between the primary and paired liver metastasis in advanced gastric cancer

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Background: Although clinical outcomes are improved with anti HER2 therapy for HER2 positive advanced gastric cancer (AGC), the relationship with HER2 related molecules and their significance for clinical outcomes are still unclear including the difference between the primary and paired liver metastasis in AGC.

Methods: A total of 58 AGC with liver metastasis were enrolled in this study from November 1995 to March 2009. We investigated HER2 protein expression by immunohistochemistry (IHC) using HercepTest (DAKO) in standard procedure and assessed according to Gastric Cancer Scoring System. HER2 positivity (3+) defined complete, basolateral or lateral membranous reactivity in > 10% of the cells. About the other molecular expressions (EGFR, c-MET, IGFR), positive expression was defined as 25% or more staining with intensity 2 or 3+. We also investigated the relationship between recurrence free survival (RFS), overall survival (OS) and HER2 related molecular expression in both primary and liver metastasis.

Results: The HER2 positivity (3+) rate of primary and liver metastasis were 11.5 (6/52) and 9.4% (5/53), respectively, and concordance rate between the primary and liver metastasis was 91.4% (53/58). The EGFR positivity rate of primary and liver metastasis were 1.7% (1/57) and 5.4% (3/55), respectively, and concordance rate between the primary and liver metastasis was 93.1% (54/58). The c-MET positivity rate of primary and liver metastasis were 44.8 (26/32) and 45% (18/40), respectively, and concordance rate between the primary and liver metastasis was 75.8% (44/58). The IGFR1 positivity rate of primary and liver metastasis were 45 (18/40) and 41.4% (17/41), respectively, and concordance rate between the primary and liver metastasis was 70.6% (41/58). Median RFS and OS were 7.3 months (6.2-11.8) and 34 months (16.2-41.7), respectively. There were no relationships between any HER2 related molecular expressions and RFS, OS in both primary and liver metastasis.

Conclusions: EGFR and HER2 were high concordance rate between the primary site and liver metastasis, respectively. There were no relationships between any HER2 related molecular expressions and clinical outcomes in this cohort.

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Disclosure: All authors have declared no conflicts of interest.

Table: 693P

Covariate	b	HR	CI 95%	p-value
Surgery of metastases	−0.55115	0.5763	0.4321- 0.7686	0.000176
HER2 positive	−0.24671	0.7814	0.6654- 0.9176	0.002627
Triplet chemotherapy	−0.10337	0.9018	0.7966-1.0208	0.102276
ECOG PS ≥ 2	0.60646	1.8339	1.5660-2.1477	<0.00001
Grade 1 (vs 2-3)	−0.35216	0.7032	0.5780-0.8555	0.000432
Ascites	0.17576	1.1922	1.0441-1.3612	0.009363
Neutrophil-to-lymphocyte ratio	0.36245	1.4368	1.2771-1.6166	<0.00001
Lauren, diffuse subtype	0.05892	1.0607	0.9388-1.1984	0.344254
Surgery of the primary tumor	−0.25811	0.7725	0.6812-0.8760	<0.00001
Assessment of tumor response Partial or complete response Progressive disease Stable disease Non-measurable disease	− -0.30910 1.18294 0.02622 0.37498	− 0.7341 3.2640 1.0266 1.4550	− 0.6286-0.8574 2.7003-3.9453 0.8712-1.2097 1.1215-1.8877	− <0.00001 <0.00001 0.754166 0.004760

695P Real world data about clinical efficacy and safety of apatinib in the treatment of advanced gastric cancer

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Background: Observation study is difference with randomized controlled trial and reflects the real world data in clinical practice with larger sample size, wider inclusion criteria, various interventions and long-term follow-up. We analyzed the real world data achieve real world evidence, which was applied to analyze discuses, patients, treatment patterns, resource utilization and outcome. The aim of this study was to evaluate the efficacy and safety of apatinib in real world, and provide a decision reference for Clinical practice.

Methods: This was a prospective, multicenter, non-intervention registered study. The patients (pts), were ≥18 years old, with histologically confirmed advanced gastric cancer (GC) or adenocarcinoma of esophagogastric junction (AEG), two or more lines of prior chemotherapy. All the pts were orally given apatinib at an initial dose of 500 mg until disease progression or death. Dose adjustment was allowed.

Results: The 230 pts, included 164 males and 66 female were eligible, the average age of pts was 62 years old, stage IV was the mainly clinical stage, the main ECOG performance status was 1, 54.78% pts were given apatinib 500 mg qd. 63.91% pts were received chemotherapy along with apatinib. In the 230 pts, there were 125 received efficacy evaluation. 8 pts achieved partial response (PR), 64 had stable disease (SD), and 53 had progressive disease (PD). The objective response rate (ORR) was 6.4% and the disease control rate (DCR) was 57.6%. The middle progression free survival (mPFS) and middle overall survival (mOS) were 3.3 months and 6.3 months, respectively. Compared with the non chemotherapy, chemotherapy achieved a longer mPFS (3.8months VS 2.9 months) and mOS (8.3months VS 5.0 months). 211 pts were included for safety analysis. The incidence of adverse events (AEs) was 91.2%, The grade 3 and 4 was 62.3%. The incidence of serious adverse events (SAE) was 17.2%. Main AEs were hypertension, Hand-foot syndrome, proteinuria and fatigue. Pts received chemotherapy achieved a better tolerance.

Conclusions: The real world data show that apatinib treatment significantly improved OS and PFS with an acceptable safety profile in patients with advanced gastric cancer.

Clinical trial identification: ChiCTR-OPN-15006601

Legal entity responsible for the study: Jiang Su Cancer Hospital

Funding: None

Disclosure: All authors have declared no conflicts of interest.

696P Correlation between SPARC expression and efficacy of nab-paclitaxel for advanced gastric cancer refractory to fluoropyrimidine: An exploratory analysis of a phase II trial, CCOG1303

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Background: Secreted protein acidic and rich in cysteine (SPARC) reportedly influences the response to albumin-bound paclitaxel due to its characteristics of albumin-binding matrix-associated protein that may enhance the drug accumulation in the tumor tissue. However, its role in gastric cancer (GC) has been controversial. In this study, correlation between SPARC expression and the efficacy of nab-paclitaxel (nab-PTX) for GC was evaluated to explore its potential as a predictor of sensitivity.

Methods: In a multi-institutional prospective phase II trial (CCOG1303), efficacy of nab-PTX under a modified dose reduction criteria was evaluated in 47 advanced GC patients refractory to fluoropyrimidine. Correlation between SPARC expression on immunohistochemistry and efficacy endpoints was evaluated as a predetermined exploratory analysis in the CCOG1303 trial. SPARC staining was scored in two compartments: cancer associated fibroblasts (CAF) in the tumor stroma and tumor epithelial cells.

Results: The SPARC expression in the tumor epithelia was higher than that in the non-tumorous epithelia in only 5 patients (11%), while negative or weaker SPARC staining in the tumor epithelia was observed in the remaining specimens. SPARC expression level in the CAF was classified into the following 3 categories: 1/3 or less (score 0), 1/3∼2/3 (score 1+), and 2/3 or more (score 2+) of CAF were positive for SPARC [18 patients (38%), 11 (23%), and 18 (38%), respectively]. There was no difference according to clinicopathological characteristics between CAF SPARC level [low (score 0) vs. high (score 1+/2+)]. CAF SPARC level (low vs. high) was not associated with the progression free survival (median, 4.8 vs. 3.0 months; $P = 0.259$), overall survival (median, 10.2 vs. 8.0 months; $P = 0.419$), time to treatment failure (median, 4.7 vs. 3.0 months; $P = 0.291$), and overall response rate (0 vs. 25%; $P = 0.850$).

Conclusions: SPARC level was not correlated with efficacy of nab-PTX for GC. The results of this exploratory analysis do not support the possibility of SPARC expression level for clinical biomarker regarding nab-PTX in GC.

Clinical trial identification: UMIN Clinical Trials Registry Registration Number: UMIN000012247

Legal entity responsible for the study: Chubu Clinical Oncology Group

Funding: None

Disclosure: Y. Kodera: Honoraria: Olympus, Chugai Pharma, Lilly, Johnson & Johnson, Ajinomoto, Takeda, Yakult Honsha, Taiho Pharmaceutical, Otsuka, Kaken Pharmaceutical, Ono Pharmaceutical, Asahi Kasei, Covidien/Medtronic All other authors have declared no conflicts of interest.

697P Detection of microsatellite instability (MSI) with a novel panel of biomarkers in gastric cancer samples

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Background: Detection of microsatellite instability (MSI) is recommended to identify colorectal cancer (CRC) patients with Lynch syndrome, but MSI is present in several other tumor types such as ovarian and gastric cancer. Current clinical reference methods to detect MSI stain for mismatch repair proteins or analyze frequently mutated DNA repeat regions. The Idylla™ MSI Test is being developed for a unique set of novel biomarkers (Zhao et al. 2014; eLife) capable of faster detection with greater specificity and selectivity compared to current methods.

Methods: To assess the suitability of the novel marker set to detect MSI status in gastric cancer, we performed a small-scale evaluation study: 10 novel MSI biomarkers with proven efficacy in CRC were tested in 150 gastric cancer samples. Repeat length was determined on FFPE DNA by PCR followed by melting curve analysis. Eighty-five samples were screened with a reference methodology for MSI detection (Promega MSI analysis system).

Results: Fifteen out of 150 samples (10%) were classified as MSI-H with the novel set of biomarkers. At least 5/10 (50%) of the markers scored mutant in each of these 15 samples. All of the 10 markers scored wild type in 131/150 samples. All samples with at least one mutant marker ($n = 19$) and 66 randomly selected samples with no mutant markers were screened with the Promega MSI analysis system. 9/85 samples failed with the reference method, even after repeat testing, while the Idylla™ methodology did not generate any failures (0/150). For 76 samples with results available for both methods, the overall percent agreement was 100% (76/76).

Conclusions: Fifteen out of 150 samples (10%) were classified as MSI-H with the novel set of biomarkers. At least 5/10 (50%) of the markers scored mutant in each of these 15 samples. All of the 10 markers scored wild type in 131/150 samples. All samples with at least one mutant marker ($n = 19$) and 66 randomly selected samples with no mutant markers were screened with the Promega MSI analysis system. 9/85 samples failed with the reference method, even after repeat testing, while the Idylla™ methodology did not generate any failures (0/150). For 76 samples with results available for both methods, the overall percent agreement was 100% (76/76).

Legal entity responsible for the study: Biocartis NV, Mechelen, Belgium

Funding: EMD Serono Research & Development Institute, Inc.

Disclosure: B. De Craene: Employee with Biocartis. Z. Feng: Employee EMD Serono, a business of Merck KGaA, Darmstadt, Germany. Eligible for the Merck KGaA Long-Term Incentive Award. Stock owner of Argos Therapeutics Inc. (ARGS). Member of American society of clinical pathologists (ASCP). E. Rondelez: Employee with Biocartis. L. Vandenbroeck: Employee with Biocartis. K. Peeters: Employee with Biocartis. G. Maertens: Employee with Biocartis. E. Sablon: Employee with Biocartis. T. Cai: Employee with EMD Serono, a business unit of Merck KGaA, Darmstadt, Germany.

698P A dose-response study of ramucirumab treatment in patients with gastric cancer/gastroesophageal junction adenocarcinoma: Primary results of 4 dosing regimens in the phase 2 trial I4T-MC-JVDB

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Background: Ramucirumab (RAM) is approved for the treatment of advanced gastric cancer or gastroesophageal junction adenocarcinoma with disease progression after prior platinum and/or fluoropyrimidine chemotherapy at 8 mg/kg every 2 weeks (Q2W) based on results of 2 phase 3 trials. Exposure-response analyses from these trials indicated efficacy of RAM correlated with exposure. JVDB is an open-label RAM monotherapy study that examined pharmacokinetics (PK) and safety of the standard and 3 higher exposure regimens.

Methods: Patients (n = 164) were randomized 1:1:1:1 to 4 treatment arms: 8 mg/kg Q2W (Arm 1), 12 mg/kg Q2W (Arm 2), 6 mg/kg every week (Arm 3), and 8 mg/kg Days 1 and 8 (D1D8) every 3 weeks (Q3W) (Arm 4). PK was collected from all groups. Treatment-emergent adverse events (TEAEs) were graded by NCI CTCAE v4.0. Tumor response was assessed by RECIST 1.1.

Results: Mean RAM trough and peak concentrations are shown (Table). Median (months) progression-free survival (PFS) was similar across all arms (Arm 1=1.45; Arm 3=1.54; Arm 4=1.51), with the exception of Arm 2=2.50. PFS hazard ratio (HR) for Arm 2 vs 1=0.82; Arm 3 vs 1=0.88; Arm 4 vs 1=0.77. Overall survival (OS) HR for Arm 2 vs 1=0.70; Arm 3 vs 1=0.95; Arm 4 vs 1=0.90. The most common TEAEs were fatigue (22.4%), decreased appetite (21.1%), abdominal pain (18%), and vomiting (18%), consistent with the REGARD trial.

Table: 698P

		Trough (µg/ml)		Peak (µg/ml)	
Arm	**Regimen**	**Week 6**	**Week 12**	**Week 6**	**Week 12**
1	8 mg/kg Q2W (standard)	47.6	64.3	189	195
2	12 mg/kg Q2W	71.0	79.4	303	309
3	6 mg/kg QW	83.0	125	187	226
4	8 mg/kg D1D8 Q3W	57.4	81.6	180	210

Conclusions: Trough concentrations of the 3 experimental regimens were greater than the standard regimen. Arm 2 displayed the highest peak RAM concentration. Though efficacy findings were not significant, some trends toward improved PFS and OS versus the standard regimen were observed. Despite higher RAM exposures observed with the alternative regimens, safety profiles were comparable to the standard regimen.

Clinical trial identification: NCT02443883

Legal entity responsible for the study: Eli Lilly and Company

Funding: Eli Lilly and Company

Disclosure: J.A. Ajani: Honoraria: Lilly, Bayer, Novartis, Five Prime Therapeutics, Taiho, Genentech, Celgene Funding: Novartis, BMS, Taiho, Genentech, MedImmune, Amgen, Lilly, Merck, Delta-Fly, Gilead Sciences, Takeda, Celgene. M. Shenker: Corporate-sponsored research, meaning international clinical trials (like JVDB trial), for which I have financial contract as PI: Eli Lilly, Pfizer, Roche, Novartis, BMS, MSD, Merck Serono, Boehringer Ingelheim, Amgen, Astellas, Mylan. C. Tournigand: Honoraria from Eli Lilly. D. Ferry, Y. Zhang, A. Long, W-L. Kuo, L. Gao, J. Kauh: Employee of Eli Lilly. All other authors have declared no conflicts of interest.

699P The effectiveness of the 8th American Joint Committee on Cancer TNM classification in the prognosis evaluation of stage III gastric cancer patients: A comparative study between the 7th and 8th editions

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Background: The 8th edition of the AJCC TNM staging system for gastric cancer was released in 2016 and included major revisions, especially of stage III. We aimed to compare the prognostic value of the seventh and eighth editions of the AJCC TNM classification for stage III gastric cancer.

Methods: Clinical data on 1,579 patients operated on for stage III gastric cancer according to the seventh edition between December 2006 and November 2014 were analyzed and the 7th and 8th TNM classifications were compared in terms of prognostic performance.

Results: According to the 8th AJCC TNM classification, the 5-year overall survival rates of IIIA, IIIB and IIIC were 49.4%, 29.6% and 15.2%, respectively (P<0.001). The median number of lymph nodes (LNs) resected was 33 (range 5-112), and the optimal cut-off value for the number of LNs resected was 30. Cox regression multivariate analysis showed the 8th AJCC N classification, 8th AJCC T classification, tumor size, lymphatic vessel invasion, and number of LNs removed were independent prognostic factors. However, the 7th edition classification had higher c-index, linear trend and likelihood ratioχ2 scores, and smaller AIC values compared with those for the 8th edition, which represented the optimum prognostic stratification. Further subgroup analysis found that the 8th staging system generated the best prognostic stratification only when LNs removed≥30.

Conclusions: The 8th TNM classification provide better accuracy than 7th edition in predicting the prognosis of stage III gastric cancer with LNs harvested≥30.

Legal entity responsible for the study: Changming Huang

Funding: None

Disclosure: All authors have declared no conflicts of interest.

700P Comparison of prognostic models for hepatocellular carcinoma (HCC) in patients treated with the sorafenib: Results from a Canadian multi-center HCC database

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Background: Several staging systems and models (TNM, BCLC, Okuda, CLIP and ALBI) have been developed to estimate the prognosis of patients with HCC. Most of these were developed prior to the prevalent use of sorafenib. The purpose of this study was to compare the prognostic and discriminatory power of these models in predicting survival for HCC patients treated with sorafenib.

Methods: Patients who received sorafenib for the treatment of HCC between January 1, 2008 and June 30, 2015 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. Survival outcomes for each model were assessed with Kaplan-Meier (KM) curves and compared with the log-rank test. Time dependent area under the curve (t-AUC) was used to test the discriminatory power of each model (higher t-AUC = more discriminatory power). Akaike information criterion (AIC), a measure of goodness-of fit of models while penalizing overly complex models, was used to compare the models (lower AIC = better model).

Results: A total of 681 patients were included in this analysis. Median age was 64 years (range 8-91). Majority were males (80%), had a Child-Pugh score A (86%), ECOG performance status 0 (30%) and 1 (60%). 37% of patients were of East Asian ethnicity. Most common etiology for liver disease was hepatitis B (33%) and C (29%). At start of sorafenib, most patients were BCLC stage C (92%) and TNM stage IV (61%). The median overall survival for the entire cohort was 9.2 months (95% CI 8-10.4). CLIP had the highest t-AUC and the lowest AIC. See table below for t-AUC and AIC results.

Table: 700P

Prognostic model	AIC	t-AUC (95% CI)
CLIP	5725.76	0.659 (0.601 – 0.718)
Okuda	5730.38	0.645 (0.597 – 0.694)
ALBI	5756.73	0.558 (0.510 – 0.599)
BCLC	5759.25	0.558 (0.518 – 0.599)
TNM stage	5771.51	0.561 (0.499 – 0.623)

Conclusions: According to our large multi-center study, CLIP appears to be the most informative in predicting survival in HCC patients treated with sorafenib. Prospective studies are needed to determine its role in patient selection for clinical trials and in guiding treatment decisions. The TNM and BCLC staging systems were the least useful in predicting survival in this population.

Legal entity responsible for the study: CHORD Consortium

Funding: None

Disclosure: All authors have declared no conflicts of interest.

701P Final data from a phase Ib trial of tepotinib in Asian patients with advanced hepatocellular carcinoma (HCC)

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Background: Therapeutic outcomes for patients (pts) with advanced hepatocellular carcinoma (HCC) are currently poor, despite the introduction of new therapies. c-Met is a potential therapeutic target in HCC, and c-Met inhibitors have demonstrated activity in preclinical HCC models. Tepotinib (MSC2156119J) is a highly selective c-Met inhibitor that has favorable safety and promising clinical activity, particularly against c-Met+ solid tumors. We report the final results of a phase Ib trial of tepotinib in pts with advanced HCC.

Methods: Enrolled pts were Asian adults with confirmed HCC of BCLC Stage C, Child-Pugh Class A liver function without encephalopathy, and ECOG PS 0–2. Pts received tepotinib 300, 500 (the RP2D), or 1,000 mg/day on a 21-day cycle. c-Met expression was retrospectively determined by IHC (c-Met+ defined as $\geq$ 50% tumor IHC2+/3+). The primary objective was to confirm the recommended phase II dose (RP2D) of tepotinib.

Results: No dose-limiting toxicities were observed in the 27 pts enrolled (median age 57 [38-69]; male 23; ECOG PS 0/1 11/16), who received tepotinib 300 mg/day (n = 7), 500 mg/day (n = 14), or 1,000 mg/day (n = 6, 3 with dose reduction). 22 pts had treatment-related treatment-emergent adverse events (TRTEAEs), most commonly diarrhea (n = 10), nausea (n = 8), elevated AST (n = 7), and elevated ALT (n = 6). The most common grade $\geq$3 TRTEAEs were elevated AST (n = 3), elevated ALT (n = 3), and elevated lipase (n = 3). Best overall response (BOR) was partial response (PR) in 2 pts, of duration 19.0 months (500 mg) and 4.4 months (1,000 mg). 8 pts had a BOR of stable disease (SD), 14 pts had PD, 1pt had Non-CR/Non-PD, 2pts were not evaluable. 5 pts had progression-free survival >8 months. Tumor c-Met status was available for 26 pts; of 7 pts with c-Met+ tumors, 2 had a PR and 2 had SD. PK and exploratory biomarkers were investigated.

Conclusions: Tepotinib had antitumor activity in Asian pts with advanced HCC, particularly those with c-Met+ tumors, and was well tolerated at doses up to 1,000 mg/day. A maximum tolerated dose was not defined. The efficacy and safety of first-line tepotinib in pts with c-Met+ HCC are being compared with those of sorafenib in the phase II part of this study.

Clinical trial identification: NCT01988493

Legal entity responsible for the study: Merck KGaA

Funding: Merck KGaA

Disclosure: D. Zhou, C. Zhao, A. Becker: Employee of Merck. All other authors have declared no conflicts of interest.

702P Correlation between overall survival (OS) and time to progression (TTP) and between OS and response rate (RR) by RECIST in advanced hepatocellular carcinoma (HCC)

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Background: TTP and RR have been suggested as potential surrogate endpoints for OS in advanced HCC. Here, we report correlation between OS and TTP/RR using simulated trials based on patient-level data from the phase 3 SHARP and AP trials in patients with advanced HCC randomized to sorafenib (SOR) or placebo (PBO).

Methods: A bootstrap approach was applied to simulate 10,000 trials of patients with advanced HCC from SHARP (N = 602; NCT00105443) and AP (N = 226; NCT00492752). RR was measured by investigator assessment per RECIST with SHARP–BCLC amendments (Reig et al. Semin Liver Dis 2014) prior to crossover of PBO subjects to SOR treatment. Pearson correlation was calculated between estimated median OS (mOS) and estimated median TTP (mTTP)/estimated RR for the SOR and PBO arms separately. Pearson correlation of log-rank test statistics comparing SOR and PBO were calculated for OS and TTP; Cochran–Mantel–Haenszel test statistic comparing the 2 arms for RR was also evaluated.

Results: The mean of mOS, mTTP, and RR from simulated trials was similar to that reported in SHARP and AP (Table). The correlation between mOS and mTTP was 0.270 for SOR and 0.218 for PBO in SHARP, and 0.315 for SOR and 0.258 for PBO in AP; the correlation of log-rank test statistics comparing SOR and PBO was 0.387 in SHARP and 0.581 in AP. In SHARP, the correlation between mOS and RR was 0.174 for SOR and 0.051 for PBO; the correlation of test statistics comparing SOR and PBO was 0.156. In AP, the correlation between mOS and RR was 0.138 for SOR and 0.099 for PBO; the correlation of test statistics comparing SOR and PBO was 0.211.

Conclusions: The simulated data were representative of patient population data in the SHARP and AP trials for mOS, mTTP, and RR. Our analysis showed a weak correlation between OS and TTP/RR in these trials, suggesting that TTP and RR by RECIST are not reliable surrogate endpoints for OS in patient with advanced HCC.

Clinical trial identification: NCT00105443; NCT00492752.

Legal entity responsible for the study: Bayer

Funding: Bayer

Disclosure: L. Huang, M. Shan, G. Meinhardt, K. Nakajima: Employment and stock ownership: Bayer. Y. De Sanctis: Employment and stock ownership: Bayer. J. Bruix: Research/Education Grant: Daiichi Sankyo, ArQule, Bayer, Sirtex. Honoraria: Gilead, AbbVie, Kowa, Bayer, BTG, ArQule, Terumo, Sirtex, BMS, Eisai, BI, Novartis, OSI, Roche, Onxeo. Advisory Board: Bayer, Kowa, BTG, ArQule, Terumo, Sirtex, BMS, Eisai, Novartis, OSI, Roche, Onxeo. Consulting: Gilead, AbbVie, Kowa, Bayer, BTG, ArQule, Terumo, Sirtex, BMS, BI, Kowa, Novartis, OSI, Roche, Onxeo, Daiichi Sankyo, Abbot, Glaxo, Eli Lilly. J. Llovet: Research/education grant: Bayer, Blueprint, Boehringer Ingelheim, Incyte Advisory board attendance: Bayer, Eisai, BMS, Eli Lilly Consultancy: Bayer, BMS, Blueprint, Eisai, Eli Lilly, Celsion, Boehringer Ingelheim. A-L. Cheng: Honoraria, advisory board attendance, consulting: ONO Pharmaceuticals, BMS, Merck, MSD, Novartis, Bayer.

703P Cost effectiveness of selective internal radiation therapy (SIRT) with Y-90 resin microspheres versus sorafenib in Barcelona Clinic Liver Cancer (BCLC) stage C hepatocellular carcinoma patients in the UK

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Background: Recently presented pivotal trial data (Vilgrain *et al. International Liver Congress 2017*) has shown that there is no significant difference in overall survival between selective internal radiation therapy (SIRT) with Y-90 resin microspheres (SIR-Spheres®; Sirtex Medical, North Sydney, Australia) and sorafenib for patients with Barcelona Clinic Liver Cancer (BCLC) stage C liver-limited or liver-predominant hepatocellular carcinoma. Y-90 resin microspheres are, however, safer and better tolerated by patients than sorafenib, as well as reducing costs, due to single administration and less frequent and severe side effects. Our aim was to evaluate the cost effectiveness of SIRT using Y-90 resin microspheres versus sorafenib for the treatment of patients with BCLC stage C hepatocellular carcinoma in the UK.

Methods: A cost-minimisation model was built, with equal efficacy assumed between Y-90 resin microspheres and sorafenib. Adverse events data were collected from the Phase III SHARP trial for sorafenib (Llovet *et al. N Engl J Med* 2008;359:378–90) and from the ENRY study for Y-90 resin microspheres (Sangro *et al. Hepatology* 2011;54:868–78). Treatment costs were taken from standard UK sources and real-world data from a UK hospital; treatment and adverse events disutilities were taken

Table: 702P

Trial	Treatment	mOS, days	Simulated data Mean (SD) of mOS, days	mTTP, days	Simulated data Mean (SD) of mTTP, days	RR	Simulated data Mean (SD) of RR
SHARP	Sorafenib	327	329 (26.5)	119	118 (10.1)	0.057	0.057 (0.013)
	Placebo	243	245 (21.7)	82	83 (2.4)	0.023	0.023 (0.009)
AP	Sorafenib	198	198 (18.8)	84	85 (6.4)	0.033	0.033 (0.014)
	Placebo	127	129 (14.5)	42	42 (2.5)	0.013	0.013 (0.013)

m, median; SD, standard deviation

from published literature. Inputs were validated by UK clinicians and one-way and probabilistic sensitivity analyses were performed.

Results: SIRT using Y-90 resin microspheres is dominant versus sorafenib, providing greater quality-adjusted life years (QALYs) at a lower cost. Y-90 resin microspheres provide 0.0079 (95% confidence interval [CI] 0.0046–0.0111) more QALYs than sorafenib, while saving £8,909 (95% CI £3,257–£14,570). One-way sensitivity analysis showed time on treatment for sorafenib and the work-up and administration costs of Y-90 resin microspheres to be the parameters with the largest influence on results.

Conclusions: In the case of equal efficacy between Y-90 resin microspheres and sorafenib, SIRT using Y-90 resin microspheres is a cost-effective therapy for BCLC stage C hepatocellular carcinoma patients in the UK.

Legal entity responsible for the study: BresMed Health Solutions Ltd

Funding: Sirtex

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704P Ang-2 polymorphisms in relation to outcome in advanced HCC patients receiving sorafenib

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Background: Sorafenib, an oral multikinase inhibitor, represents the standard care for advanced hepatocellular carcinoma. Angiopoietin-2 (Ang-2) is a crucial angiogenic factor. By binding to its receptor Tie2, Ang-2 cooperates with the VEGF pathway to maintain normal physiological functions. In the presence of VEGF, Ang-2 destabilizes blood vessels and promotes vascular sprouting. In cancers, Ang-2 is linked to not only angiogenesis but also invasive and metastatic phenotypes. Although sorafenib exerts no significant activity against Tie2, the predictive value of Ang-2 has been explored in 2 studies. The actual role of Ang-2 in predicting sorafenib efficacy warrants further investigations. Polymorphism analysis seems to have more advantages than protein or gene expression analysis. In our study we analysed the role of ANG-2 polymorphisms in relation to clinical outcome in patients with hepatocellular carcinoma treated with sorafenib.

Methods: We analyzed 135 patients with hepatocellular carcinoma treated with sorafenib. Peripheral blood samples or FFPE tumor tissues were available for DNA extraction and genotyping analysis. Nine Ang-2 polymorphisms were analyzed by direct sequencing or Real Time PCR method.

Results: With regard to Ang4 rs55633437 was observed that patients carrying the allele GG were associated with a better PFS and OS. The variants GG were associated with a median OS of 16.9 months vs 6.5 months of variants GT and TT ($p = 0.016$). The variants GT and TT were associated with a median PFS of 2.94 months vs 4.67 months of variants GG ($p = 0.03$). These data were confirmed by multivariate analysis.

Conclusions: Ang4 rs55633437 could represent prognostic markers in patients with advanced hepatocellular carcinoma treated with sorafenib.

Legal entity responsible for the study: IRST-IRCCS

Funding: None

Disclosure: All authors have declared no conflicts of interest.

705P Circulating miRNA biomarkers predicting regorafenib (REG) clinical benefit in patients with hepatocellular carcinoma (HCC) in the RESORCE trial

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Background: REG improved overall survival (OS) and time to progression (TTP) versus placebo in patients with HCC who progressed during prior sorafenib in the phase 3 RESORCE trial (Bruix et al, *Lancet* 2017). This exploratory analysis evaluated the potential of circulating miRNA plasma biomarkers to predict the OS and TTP benefit with REG in RESORCE.

Methods: Valid biomarker data were available for 343/573 patients. Expression levels of 750 plasma miRNAs collected at baseline were quantified by qPCR. To be eligible, miRNAs had to be measurable on a continuous scale or dichotomized by pre-processing (present vs absent), and present in $\geq 5\%$ of patients (i.e. $n \geq 18$). The predictive and prognostic effects (HR and 95% CI) were evaluated using a Cox proportional hazards model with miRNAs as continuous or dichotomized variables. A predictive effect was modeled as an miRNA–treatment interaction effect and subjected to Akaike information criterion (AIC)-based selection to assess its association with OS and TTP.

Results: Demographic covariates were generally similar in the overall RESORCE and miRNA biomarker cohorts, except the latter had a smaller proportion of Asian patients. Of the 750 miRNAs analyzed, 25 showed a multiplicity-adjusted prognostic effect ($P \leq 0.05$) for OS. Nine miRNAs showed a multiplicity-adjusted predictive effect ($P \leq 0.05$) for OS; 3 of the 9 predictive markers were also prognostic (Table). No miRNA was found to be predictive for TTP.

Table: 705P

miRNA	miRNA predictive for OS		miRNA prognostic for OS
	HR (95% CI)	P-value	P-value
hsa-miR-15b-3p	0.37 (0.20, 0.70)	≤0.05	0.01
hsa-miR-107	0.54 (0.37, 0.81)	≤0.05	0.06
hsa-miR-320b	0.57 (0.41, 0.81)	≤0.05	0.01
hsa-miR-122-5p	1.35 (1.14, 1.60)	≤0.05	0.39
hsa-miR-374b-3p	1.36 (1.11, 1.65)	≤0.05	0.06
hsa-miR-200a-3p	1.39 (1.15, 1.68)	≤0.05	0.03
hsa-miR-30a-5p	1.47 (1.14, 1.88)	≤0.05	0.34
hsa-miR-125b-5p	1.54 (1.19, 1.99)	≤0.05	0.32
hsa-miR-645	3.16 (1.52, 6.55)	≤0.05	0.06

Conclusions: This exploratory analysis suggests that multiple miRNAs may be potentially predictive for OS in patients treated with REG. The biological role of the miRNAs in HCC as well as their potential functional correlation to treatment benefit needs to be analyzed further.

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Legal entity responsible for the study: Bayer

Funding: Bayer

Disclosure: M. Teufel, G. Meinhardt: Stocks and Employment: Bayer. H. Seidel, K. Köchert: Employment: Bayer. R.S. Finn: Consulting and Advisory Role: Bayer, Pfizer, Novartis, BMS, Eisai. J.M. Llovet: Research/Education Grant: Bayer, Blueprint Medicines, BI, Incyte Advisory Board: Bayer, Eisai, BMS, Eli Lilly Consulting: Eli Lilly, Bayer, BMS, Blueprint Medicines, Eisai, Celsion, BI. J. Bruix: Research/Education Grant: Daiichi Sankyo, ArQule, Bayer, Sirtex. Honoraria: Gilead, AbbVie, Kowa, Bayer, BTG, ArQule, Terumo, Sirtex, BMS, Eisai, BI, Novartis, OSI, Roche, Onxeo. Advisory Board: Bayer, Kowa, BTG, ArQule, Terumo, Sirtex, BMS, Eisai, Novartis, OSI, Roche, Onxeo. Consulting: Gilead, AbbVie, Kowa, Bayer, BTG, ArQule, Terumo, Sirtex, BMS, BI, Kowa, Novartis, OSI, Roche, Onxeo, Daiichi Sankyo, Abbot, Glaxo, Eli Lilly.

706P Overall survival (OS) by platelet count at baseline in patients with hepatocellular carcinoma (HCC) treated with sorafenib (SOR) in the SHARP and AP trials and regorafenib (REG) in the RESORCE trial

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Background: SOR and REG significantly improved OS versus placebo (PBO) in patients with unresectable HCC: SOR in the first-line setting in both the SHARP (median OS: 10.7 SOR vs 7.9 months PBO, HR 0.69; $P < 0.001$) and AP trials (median OS: 6.5 SOR vs 4.2 months PBO, HR 0.68; $P = 0.014$); and REG in patients who progressed during prior SOR in the RESORCE trial (median OS: 10.6 REG vs 7.8 months PBO, HR 0.63; $P < 0.0001$). This exploratory analysis evaluated OS by baseline platelet count in HCC in the SHARP, AP, and RESORCE trials.

Methods: Patients with advanced HCC who received treatment in SHARP (SOR $n = 299$, PBO $n = 303$; NCT00105443), AP (SOR $n = 150$, PBO $n = 76$; NCT00492752), and RESORCE (REG $n = 374$, PBO $n = 193$; NCT01774344) were included in the analysis. Patients were subgrouped according to a baseline platelet count of $> 150 \times 10^9$/L and $\leq 150 \times 10^9$/L. OS (HR and its 95% CI) was evaluated using a Cox proportional hazards model.

Table: 706P

Trial (active drug)	Platelet count	n	Median OS for active drug, days	Median OS PBO, days	HR* (95% CI)
SHARP (SOR)	$>150 \times 10^9$/L	379	290	218	0.81 (0.63, 1.04)
	$\leq 150 \times 10^9$/L	221	442	297	0.60 (0.42, 0.85)
AP (SOR)	$>150 \times 10^9$/L	130	186	119	0.62 (0.42, 0.93)
	$\leq 150 \times 10^9$/L	95	227	166	0.78 (0.47, 1.31)
RESORCE (REG)	$>150 \times 10^9$/L	254	326	230	0.57 (0.41, 0.78)
	$\leq 150 \times 10^9$/L	318	313	241	0.78 (0.58, 1.04)

*HR < 1 indicates superiority of SOR/REG over PBO.

Results: In SHARP, 180 patients (60%) treated with SOR and 199 (66%) receiving PBO had a baseline platelet count of $> 150 \times 10^9$/L; 84 (56%) with SOR and 46 (61%) with PBO in AP; 163 (44%) with REG and 91 (47%) with PBO in RESORCE. Baseline variables were generally similar between subgroups for AP; in RESORCE, more patients had hepatitis C in the $>150 \times 10^9$/L platelet count group; in SHARP, the lower platelet count group had more patients with ECOG PS 0 and BCLC B, fewer patients with macrovascular invasion and extrahepatic spread, less tumor burden, and more cases of hepatitis C. In SHARP and AP, a lower platelet count at baseline was associated with improved OS, but this was not observed in RESORCE. Both SOR and REG improved OS over PBO in both subgroups.

Conclusions: The analysis indicates that platelet count may be a prognostic factor for first-line HCC but not for second-line HCC patients. SOR and REG are effective treatment options in HCC regardless of platelet count at baseline.

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Legal entity responsible for the study: Bayer

Funding: Bayer

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707P Network meta-analysis (NMA) of treatments for unresectable hepatocellular carcinoma (uHCC)

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Background: In a phase 3 randomized controlled study (RCT) lenvatinib (LEN) demonstrated significantly better progression-free survival (PFS) vs sorafenib (SOR) in treatment-naive (1L) uHCC patients. Prior SOR RCTs had been conducted vs placebo (PBO). Our aim was to synthesize all efficacy evidence enabling a comparison of both LEN and SOR to PBO.

Methods: EMBASE®, MEDLINE®, MEDLINE® in-process, and Cochrane databases were systematically searched through February 2017 for relevant RCTs in 1L uHCC. Data from the recently completed LEN RCT were added to the review. A conventional NMA based on PFS and overall survival (OS) was performed using a frequentist random effect NMA programmed in R-3.3.1. PBO was used as the reference treatment.

Results: 3 Studies met inclusion criteria: 1 recently completed LEN vs SOR study (N = 954) and 2 RCTs comparing SOR to PBO: (1) Llovet 2008 (N = 602) and (2) Cheng 2009 (N = 226). The 3 RCTs were generally comparable with some variability in patient baseline characteristics: mean age, years (63, 66, 61), % male (84, 87, 85), % ECOG score 0-1 (100, 93, 95), % Child–Pugh class A (99, 97, 97), and % prior hepatitis B/C (50/23, 19/28, 73/8) in LEN vs SOR, SOR vs PBO (1), and SOR vs PBO (2), respectively. In the NMA vs PBO, LEN and SOR yielded indirect hazard ratios (HRs) of 0.38 and 0.58 for PFS and 0.63 and 0.69 for OS, respectively. Using LEN as a common comparator, SOR and PBO yielded indirect HRs of 1.52 and 2.63 for PFS and 1.09 and 1.58 for OS, respectively (Table).

Table: 707P

Intervention	PFS HR (95% CI)	OS HR (95% CI)
PBO – Comparator		
LEN	0.38 (0.30; 0.49)	0.63 (0.50; 0.80)
SOR	0.58 (0.47; 0.70)	0.69 (0.57; 0.83)
LEN – Comparator		
SOR	1.52 (1.30; 1.76)	1.09 (0.94; 1.26)
PBO	2.63 (2.06; 3.36)	1.58 (1.25; 2.00)

Conclusions: This NMA demonstrated that for 1L uHCC patients, both LEN and SOR demonstrated significantly better PFS vs PBO: 62% progression risk reduction for LEN vs 42% for SOR.

Legal entity responsible for the study: Eisai Inc

Funding: Eisai Inc

Disclosure: G. Meier, D. Misurski, M. Baig, T. Tamai: Employee of Eisai Inc. S. Kraljevic: Employee of Eisai Co Ltd. All other authors have declared no conflicts of interest.

708P Epidemiological study of histologically proven advanced hepatocholangiocarcinoma: An AGEO multicenter retrospective study

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Background: Hepatocholangiocarcinoma (cHCC-ICC) is a rare primary hepatic tumor combining the features of cholangiocarcinoma and hepatocellular carcinoma. Few data about the epidemiology of cHCC-ICC have been reported, mainly from surgical series in Asian and American populations. The aim of this study was to evaluate epidemiological features and overall survival (OS) of histologically proven advanced cHCC-ICC patients.

Methods: Data from patients treated for histologically proven cHCC-ICC in six French university hospitals between 2008 and February 2017, were retrospectively collected. The main clinical, biological, treatment and follow up data were reported. Statistical analysis was performed using Graph Pad Prism 6.

Results: Thirty patients were included (76.6% of men, median age 64 years [extreme 37-88]). Cirrhosis was associated in 33.3% of cases (Child-Pugh score A: 70%). Positive serology for hepatitis B virus and C was found in respectively, 5 (16.6%) and 2 (6.6%) patients; with 1 co-infection. Chronic alcoholism was noted in 33.3%, diabetes and obesity were both present in 26.6% of cases. Alpha-fetoprotein, carbohydrate antigen 19-9 and carcinoembryonnic antigen serum levels were above normal in respectively 39% (median = 5.3 µg/L [2 – 21 479]), 50% (median = 21.8 IU/mL [4.5-20 000]) and 14% (median = 2.4 µg/L [2-88]) of cases. Six patients (20%) were initially treated by surgical resection. At the diagnosis of advanced disease, 66.6% of patients had multifocal hepatic lesions, 50% distant metastases (bone (23.3%), lung (20%), peritoneal metastases (13.3%)). Twenty-seven patients (90%) received first line of systemic treatment. Twenty-four patients were treated by chemotherapy: Gemcitabine (Gem) alone (n = 1), Gem+oxaliplatin (Gemox) (n = 12), Gemox + bevacizumab (n = 9), Gem+cisplatin (n = 2). Two patients received chemoembolization, 1 patient received sorafenib. Twenty-one (70%) and 4 (13.3%) patients had a second and third line of treatment, respectively. Median OS was 14.5 months.

Conclusions: Advanced cHCC-ICC appear to be aggressive tumors with a poor prognosis. Cirrhosis was associated in one third of cases. Systemic treatments are not standardized and must be evaluated in a dedicated study.

Legal entity responsible for the study: Dr. Yann Touchefeu

Funding: None

Disclosure: All authors have declared no conflicts of interest.

709P A Phase II study of sorafenib and yttrium-90 glass microspheres for advanced hepatocellular carcinoma, BCLC stage C

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Background: Combined use of sorafenib and local therapy for treating unresectable hepatocellular carcinoma (HCC) is not well established. Notably, most common cause of death in HCC is liver failure, therefore we tested the promise of controlling the local tumors even in the setting of advanced/metastatic disease to improve survival. Our study aimed to assess the efficacy and safety of combined use of sorafenib and yttrium-90 resin microspheres (Y90 RMS) in unresectable HCC defined as Barcelona Clinic Liver Cancer class C.

Methods: Between October 2013 and August 2016 we enrolled 40 advanced stage HCC patients, 38 patients were treated with sorafenib followed (after 4 weeks) with Y90 RMS at MD Anderson Cancer Center. Survival analysis was done to evaluate median overall survival (OS) and progression-free survival (PFS). We used modified Response Evaluation Criteria in Solid Tumors (RECIST) to assess response to treatment and the Common Terminology Criteria for Adverse Events (CTCAE) v4.0 to evaluate the grading of treatment related toxicity.

Results: The majority of our patients were males (74%), white (47%), 66% of patients had underlying liver cirrhosis, 26% had vascular invasion, and 26% had extrahepatic disease. The estimated median OS and 95% confidence interval (CI) in months was 18.46 (12.29 – NA) and the estimated PFS was 12.29 months (5.72 – 18.79). Stable disease (SD) was observed in 44.74% of patients, while 28.95% achieved partial response (PR). Grade III-IV adverse events included fatigue (n = 3), hyperbilirubinemia (n = 2), thrombocytopenia (n = 1), proteinuria (n = 1), hyponatremia (n = 1), elevated liver enzymes (n = 4), hypertension (n = 4), diarrhea (n = 1), nausea (n = 1) and vomiting (n = 2).

Conclusions: This is the first prospective study to evaluate sorafenib followed by Y90 in HCC. Our study included patients with metastatic HCC and showed that combined use of sorafenib and Y90 was tolerable and was associated with longer OS and PFS compared to previous studies which evaluated sorafenib alone. However, future randomized phase III studies are warranted to assess sorafenib+/-Y90 in metastatc disease setting.

Clinical trial identification: NCT01900002

Legal entity responsible for the study: MD Anderson Cancer Center

Funding: Bayer Pharmaceutical Company

Disclosure: All authors have declared no conflicts of interest.

710P Assessing cancer risk in patients with HFE gene variants and type 1 hereditary hemochromatosis

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Background: Patients with type 1 hereditary hemochromatosis are reported to have a 20-200-fold increased risk of hepatocellular carcinoma. However, not much is known about the risk of developing non-hepatobiliary cancers in these patients or those heterozygous for HFE variants. The purpose of this study is to assess the risk of non-hepatobiliary cancers in a large cohort.

Methods: Using the Geisinger-Regeneron DiscovEHR cohort, we sequenced whole exomes of 51,289 study participants to further analyze the HFE gene variations (C2892Y, H63D or S65C) for risk of cancer development. The cancer prevalence and statistical significance was assessed in both genders from multiple HFE genotypes.

Results: There were 51, 270 participants in this study: 30, 280 (59%) women and 20, 990 (41%) men. There was an increased risk of cancer overall among patients who harbored one or more HFE gene mutation (Kruskal-Wallis; $p < 0.00001$). While most cancers occurred in patients who had no known HFE mutations (20.5%), cancers were found in patients heterozygous for H63D/WT (6.14%) and C282/WT (2.31%). When the probability of cancer among men without HFE mutations were compared to other men with varying mutant genotypes, men with one or more HFE mutations had an increased probability of cancer if: homozygous C282Y ($p < 0.0001$), compound heterozygous for C282Y/H63D ($p < 0.0001$), homozygous H63D ($p < 0.0001$), S65C/WT ($p < 0.0001$), C282Y/S65C ($p < 0.0001$), WT/C282Y ($p < 0.0053$) and not H63D/WT mutation ($p < 0.10$). Among women, only H63D/S65C and H63D/H63D mutation(s) was/were associated with an increased risk of cancer ($p < 0.0001$).

Conclusions: To our knowledge, this is the first whole exome sequencing study analyzing the HFE gene variants for cancer risk in over 50 thousand individuals. This study showed that cancer risk is increased in both HFE variants and non-HFE variants carriers and that cancer screening should be considered in this cohort.

Legal entity responsible for the study: Geisinger Medical Center and Regeneron Pharmaceuticals

Funding: Regeneron Pharmaceuticals

Disclosure: All authors have declared no conflicts of interest.

711P Selective Internal Radiation Therapy (SIRT) with Yttrium-90-glass-microspheres plus chemotherapy in first-line treatment of advanced cholangiocarcinoma (MISPHEC study)

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Background: Patients with non-resectable intra-hepatic cholangiocarcinoma (ICC) have a bad prognosis, and the efficacy of chemotherapy is limited. SIRT is a promising treatment option in hepatic tumors. In ICC there is no prospective studies of combination SIRT with chemotherapy.

Methods: This phase II single-arm study prospectively included patients with non-resectable ICC (liver-only or limited extra-hepatic disease) in 7 centers. Patients received Cisplatin 25mg/m^2 and Gemcitabine 1000mg/m^2 (reduced to 300mg/m^2 the cycles just before and following SIRT) day 1 and 8 of a 21-days cycles. SIRT was delivered during cycle 1 (unilobar disease), or cycles 1 and 3 (bilobar disease). Primary objective was response rate (RR) at 3 months according to RECIST 1.1, with the objective to show a RR > 22%. Secondary objectives were toxicity, Progression-Free Survival (PFS), Overall Survival (OS), disease control rate (DCR) and RR according to Choi criteria.

Results: 45 patients met clinical inclusion criteria, and 41 were deemed treatable with SIRT after pretreatment angiography and included in the study. 34% of patients had abdominal extrahepatic lesions, 17% had thoracic lesions, tumor was unilobar in 66%, and median CA19.9 was 1499 UI/L. Grade 3 or more hematological toxicities were seen in 27 (66%) patients, and grade 3 or more non-hematological toxicities in 21 (49%). Median number of chemotherapy cycles were 6 (range 1-15). RECIST RR was 39% [90% CI: 26-53], and DCR was 98% (all 40 evaluable patients had disease control). In the 29 patients evaluated with Choi criteria, RR was 86%. 9 patients (22%) were downstaged to surgery, with 8 (20%) achieving R0 resection. Median PFS was 13 months [95% CI: 7-NR], with 12- and 24-months PFS rates of 51% and 37%, respectively. Median OS was 21 months [95% CI: 14-NR], with 12- and 24-months OS rates of 73% and 36%, respectively.

Conclusions: Combination of chemotherapy and SIRT achieved promising activity in first-line treatment of inoperable ICC, with median PFS and OS comparing favorably with chemotherapy-only historical data, and a significant proportion of patients downstaged to surgery. Toxicity was manageable. Further studies of SIRT in ICC are warranted.

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Legal entity responsible for the study: Centre Eugene Marquis, Rennes, France

Funding: BTG

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712P Effect of adjuvant chemotherapy and chemoradiotherapy in patients with ampullary carcinoma: A NCDB analysis

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Background: Ampullary carcinoma is a rare gastrointestinal cancer and the benefit of adjuvant chemotherapy is debatable. We used the National Cancer Data Base (NCDB) to evaluate if adjuvant chemotherapy (AC) or adjuvant chemo-radiation (ACR) provides a survival benefit in patients undergoing resection.

Methods: Utilizing the NCDB from 2004-2012, 5949 patients who underwent ampullary tumor resection were identified. All patients had confirmed histological diagnosis, and follow up. Patients not considered candidates for AC or ACR were excluded. 2194 patients underwent surgical resection alone (S). This cohort was compared with 874 patients who received AC, and 1128 patients ACR. Patients were stratified into node negative (NN) or node positive (NP) disease. Overall survival (OS) was performed utilizing Kaplan-Meier method, and log-rank tests were used for statistical comparisons. Cox proportional hazards were performed to control for age, gender, race, type of facility (academic versus non-academic), income, education, Charlson-Deyo score (CDS), T size, and histologic grade. All tests were two sided and a P value of < 0.05 was considered significant.

Results: The median age at diagnosis was 65 years (range 20-90). In the NN group, median OS was not reached (NR) for AC, NR for ACR and 101 months (mo) for S ($p = 0.21$). In contrast in the NP group, median OS was 33 mo for AC, 35 mo for ACR

and 27 mo for S ($p < 0.0001$). In a multi-variate analysis of NP patients, AC or ACR were independent positive prognostic factors with Hazard Ratio 0.79 for AC (95% CI 0.68-0.9; $p = 0.0005$) and 0.76 for ACR (95% CI 0.67-0.8; $p < 0.0001$) when compared to S. No differences were seen when AC was directly compared to ACR. Older age, tumor size larger than 2 cm, poor histologic grade, high CDS, low income and black race were independent negative prognostic factors.

Conclusions: Adjuvant chemotherapy or chemoradiotherapy are associated with a significant survival benefit in patients with resected node positive ampullary carcinoma when compared to surgery alone. The addition of radiation, however, does not confer additional benefit over adjuvant chemotherapy. Patients with node negative disease do not seem to benefit from adjuvant therapy regardless of primary tumor size.

Legal entity responsible for the study: Mayo Clinic

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713P The mutational landscape of periampullary adenocarcinomas in relation to morphological subtype and patient survival

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Background: Periampullary adenocarcinomas, including pancreatic cancer, are a heterogenous group of tumours. Despite improvements in oncological treatments in recent years, these patients still suffer from a poor prognosis. Emerging evidence shows that tumour morphology, intestinal type (I-type) and pancreatobililary type (PB-type), is a more relevant prognostic factor than anatomical tumour origin. The aim of this study was to map the mutational landscape in periampullary adenocarcinomas with particular reference to tumour morphology and prognosis.

Methods: The mutational status of 70 selected genes was mapped using next generation sequencing (NGS) in primary tumours from 103 patients with periampullary adenocarcinoma from a well-characterised consecutive cohort treated with pancreaticoduodenectomy at the University hospitals in Lund and Malmö, Sweden. Microsatellite instability (MSI) status was assessed by immunohistochemistry.

Results: The 5 most common mutations were TP53 ($n = 55$, 54.5%) followed by KRAS ($n = 27$, 46.5%), NF1 ($n = 45$, 44.6%), MAP3K1 ($n = 40$, 39,6%) and FGR1 ($n = 22$, 21.8%). Morphology or MSI status did not impact the burden of mutations. High tumour burden was not associated with patient survival. In the whole cohort, 9 mutations were prognostic (CDH1, CTNNB1, ERBB3, ERBB4, FGFR1, H6PD, KRAS, SH3BP4 and STK11). In I-type tumours, 6 mutations were prognostic (CDH1, CTNNB1, GATA3, KRAS, MYC and SH3BP4) while 5 mutations were prognostic in PB-type tumours (ERBB4, H6PD, NRAS, PARP1 and STK11). Notably, PARP1 and ERBB3 mutations were associated with improved prognosis. Adjusting for clinical parameters, two mutations remained significant in PB-type tumorus; STK11 (HR = 6.25; 95% CI 1.12-35.04) and PARP1 (HR = 0.86; 95% CI 0.10-0.71). In I-type tumorus, three mutations remained significant; KRAS (HR = 4.78; 95% CI 1.33-17.15), GATA3 (HR = 15.65; 95% CI 2.72-90.26) and CTNNB1 (HR = 9.03; 95% CI 1.18-69.05).

Conclusions: The results from this study demonstrate that the prognostic impact of different mutations, e.g. KRAS, in periampullary adenocarcinoma differs by morphological subtype. Thus, morphology is an important factor to consider in the development of novel targeted therapies and in biomarker studies.

Legal entity responsible for the study: Lund University

Funding: Swedish Cancer Society, Swedish Research Council, Mrs Berta Kamprad Foundation

Disclosure: All authors have declared no conflicts of interest.

714P Gemcitabine and platinum- based chemotherapy in first line treatment of hepatocholangiocarcinoma: An AGEO multicenter retrospective study

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Background: Hepatocholangiocarcinoma (cHCC-ICC) is a rare primary hepatic tumor combining features of cholangiocarcinoma (ICC) and hepatocellular carcinoma (HCC). The aim was to evaluate the overall survival (OS), progression free survival (PFS) and prognostic factors in unresectable cHCC-ICC treated by gemcitabine (gem) and platinum- based chemotherapy in first line systemic treatment.

Methods: Data from patients treated for advanced cHCC-ICC by gem and platinum-based chemotherapy in six French university hospitals between 2008 and 2016, were retrospectively collected. The diagnosis of cHCC-ICC was based on histological analysis or, in case of typical histology of ICC or HCC, on discordant CT-Scan findings and/or tumor marker (alpha-fetoprotein, carbohydrate antigen 19-9, carcinoembryonic antigen) serum levels suggesting the alternative histology. OS and PFS were estimated by Kaplan-Meier method. Prognostic factors were analyzed by Log-rank test in univariate analysis and by Cox model in multivariate analysis. Statistical analysis was performed using Graph Pad Prism 6.

Results: Forty patients were included (70% men, median age 66 years [extremes 32-88]). cHCC-ICC was histologically proven in 55% of cases. At diagnosis, twenty-three patients (57.5%) had metastatic synchronous lesion. Twenty-nine patients (72.5%) were treated by gem + oxaliplatine (GEMOX), 9(22.5%) by GEMOX + bevacizumab, 2(5%) by gem + cisplatine. Eighteen patients (45%) received second line of treatment. In the first line, patients received a median of 10 cycles of chemotherapy (extremes 1-28). RECIST1.1 criteria were reported in 35 cases: 9 patients (25.7%) had partial response, 18 (51.4%) had stable disease, 8 (22.8%) had tumor progression at first evaluation. Median PFS and OS were 9 and 15.4 months, respectively. In multivariate analysis, significant prognostic factors of poor OS were: positive serology for hepatitis B virus and/or C (HR = 1.35 IC95% [1.13-13.24] $p = 0.031$), serum bilirubin level > 30µmol/L (HR = 1.66 IC95% [1.57-17.54] $p = 0.007$), ECOG score ≥ 2 (HR = 2.46 IC95% [2.23-61.75] $p = 0.004$).

Conclusions: These data suggest a chemosensitivity of cHCC-ICC to gemcitabine and platinum based chemotherapy.

Legal entity responsible for the study: Dr. Yann Touchefeu

Funding: None

Disclosure: All authors have declared no conflicts of interest.

715P Jab1 silencing inhibits proliferation and sensitizes to cisplatin in biliary tract cancer

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Background: Jab1 is a coactivator of c-Jun that enhances the transcriptional function of c-Jun. Jab1 is frequently overexpressed in various cancers and is associated with poor prognosis of cancer patients. Thus, Jab1 could be a potential therapeutic target in cancer. However, the role of Jab1 in biliary tract cancer (BTC) has not been studied.

Methods: We evaluated the therapeutic potential of Jab1 inhibition in BTC. In vitro studies included western blot, cell growth inhibition assays, cell cycle analysis, wound healing assays, comet assays, real-time PCR, and cycloheximide chase assays. Female Balb/c athymic nude mice were used for in vivo studies.

Results: Among eight BTC cell lines tested (SNU245, SNU308, SNU478, SNU869, SNU1079, SNU1196, HuCCT-1, and TFK-1), many showed higher Jab1 expression levels. In addition, Jab1 silencing by siRNA increased p27 expression levels. Notably, SNU478 and HuCCT-1 cells exhibited profound Jab1 knockdown and increased p27 expression by Jab1-specific siRNA transfection. Jab1 silencing induced anti-proliferative and anti-migratory effects and resulted in G1 cell cycle arrest in SNU478 and HuCCT-1 cells. Jab1 knockdown alone induced spontaneous DNA damage, resulting in anti-proliferative and anti-migratory effects. Moreover, Jab1 knockdown potentiated the anti-proliferative and anti-migratory effects of cisplatin by increasing DNA damage. Interestingly, Jab1 silencing increased PTEN protein half-life without significant increase of PTEN mRNA expression levels, resulting in increased PTEN expression and decreased AKT and Src phosphorylation. In the HuCCT-1 mouse xenograft model, stable knockdown of Jab1 by shRNA also showed anti-proliferative effects in vivo, with decreased Ki-67 expression and AKT phosphorylation and increased TUNEL and p27 expression.

Conclusions: Jab1 knockdown demonstrated anti-proliferative and anti-migratory effects in BTC cells by increasing DNA damage and stabilizing PTEN, resulting in G1 cell cycle arrest and apoptosis. In addition, Jab1 silencing potentiated the anti-proliferative effects of cisplatin by enhancing DNA damage. Our data suggest that Jab1 may be a potential therapeutic target in BTC that is worthy of further investigations.

Legal entity responsible for the study: None

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716P The nationwide cancer genome screening project in Japan, SCRUM-Japan GI-screen: Efficient identification of cancer genome alterations in advanced biliary tract cancer

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Background: We have conducted the Nationwide Cancer Genome Screening Project in Japan since April 2015 using Next Generation Sequencing in cancers of digestive system, called as the SCRUM-Japan GI-SCREEN. We evaluated the frequency of cancer genome alterations. We show the result of advanced biliary tract cancer cohort (aBC; intra hepatic bile duct (IHBD), extrahepatic bile duct (EHBD), gallbladder (GB), and ampulla of Vater (AV)).

Methods: This study is ongoing with the participation of 20 major cancer centers. Patients who plan to or receive systemic chemotherapy were eligible. DNA and RNA were extracted from FFPE tumor samples and were analyzed by the Oncomine Cancer Research Panel (OCP) which allows to detect gene mutation, copy number variant (CNV) and fusions across 143 genes in a CLIA certified CAP accredited laboratory. 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 October 31st in 2016, a total of 108 aBC samples were analyzed and the sequence with the OCP was successfully performed in 73 (67.6%). The frequent/important mutations in 73 samples of which results were available were shown in table. The druggable CNVs (≥ 7 copies) were *CDK4/6* (n = 4), *EGFR* (2), *FGFR3* (2), and *ERBB2* (1). No gene fusion was detected. Proportion of gene mutations: n (%)

Table: 716P

	IHBD n = 31	EHBD n = 27	GB n = 10	AV n = 5
KRAS	10(32)	8(26)	2(20)	2(40)
TP53	5(16)	6(19)	6(60)	2(40)
BRAF	0	1(3)	0	1(20)
PIK3CA	0	0	4(40)	0
BRCA2	0	2(6)	0	0
ATM	1(3)	2(6)	1(10)	0
IDH1	3(10)	1(3)	0	0
FGFR2/3	2(6)	0	0	1(20)
ERBB3	1(3)	3(10)	0	0

Conclusions: This nationwide screening system is efficient to detect rare gene alterations in aBC. This novel knowledge provides an intriguing background to investigate new target approaches and represents a progress toward more precision medicine.

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Legal entity responsible for the study: SCRUM-Japan GI-SCREEN

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717P Prognostic implication of inflammation-based prognostic scores in patients with intrahepatic cholangiocarcinoma (iCCA) treated with first-line Gemcitabine plus Cisplatin (GEMCIS)

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Background: There is increasing evidence that inflammation-based prognostic scores have prognostic value in several cancer types, including iCCA. However, most of the studies are focused on evaluating their value in patients with resectable disease. We retrospectively evaluated the prognostic implication of inflammation-based prognostic scores including modified Glasgow Prognostic Score (mGPS) based on serum albumin and C-reactive protein, neutrophil-lymphocyte ratio (NLR), and platelet-lymphocyte ratio (PLR) in patients with unresectable or metastatic iCCA.

Methods: Between April 2010 and May 2015, a total of 296 patients with histologically documented advanced iCCA were treated with first-line GEMCIS in Asan Medical Center, Seoul, Korea. Of these, 257 patients had complete data for inflammation-based prognostic scores and were included in this study. Primary endpoint was overall survival (OS).

Results: Median age was 59 years (range, 27-78) and 158 patients (61.5%) were male. Initially metastatic disease was the most common disease status at GEMCIS (n = 170, 66.1%) followed by recurrence after surgery (n = 44, 17.1%) and locally advanced unresectable disease (n = 43, 16.7%). With a median follow up duration of 25.0 months (95% CI, 19.6-30.4), median OS was 9.1 months (95% CI, 8.0-10.2). In univariate analyses, high mGPS and NLR scores were associated with poorer OS (mGPS 1-2 vs 0: median 6.9 vs 14.1 months, $p < 0.01$, and NLR 1-2 vs 0: 6.9 vs 11.8 months, $p < 0.01$). PLR was not associated with OS ($p = 0.39$). In the multivariate analysis including potential prognostic factors such as disease extent, number of metastatic sites, performance status and liver cirrhosis, only mGPS remained significant (1-2 vs 0; HR = 1.59, $p < 0.01$).

Conclusions: The current study suggests that mGPS might be the relevant prognostic index which can stratify the survival outcomes of patients with unresectable or metastatic iCCA who received first-line GEMCIS.

Legal entity responsible for the study: Asan Medical Center, University of Ulsan College of Medicine.

Funding: None

Disclosure: All authors have declared no conflicts of interest.

718P Phase 2 study of triplet chemotherapy with oxaliplatin, irinotecan and S-1 (OIS) as first-line treatment in patients with advanced biliary tract cancer (BTC)

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Background: Although gemcitabine plus cisplatin has been established as the standard first-line chemotherapy for patients with advanced BTC based on the success of the ABC-02 trial, the overall prognosis is still poor as median survival of less than 1 year. Therefore, we investigated novel combination of three drugs including oxaliplatin, irinotecan and S-1, oral fluoropyrimidine, (OIS) for advanced BTC.

Methods: Chemotherapy-naïve patients with histologically documented unresectable or metastatic BTC were eligible for this study. Patients received oxaliplatin 65 mg/m2 Day 1, irinotecan 135 mg/m2 Day 1, and S-1 40 mg/m2 BID Day 1-7, every 2 weeks, until the disease progression or intolerable toxicities. Primary endpoint was objective response rate (ORR) defined by RECIST v1.1 and secondary endpoints include progression-free survival (PFS), overall survival (OS) and safety profile. According to the Simon's optimal two-stage design with type 1 error of 0.05 and a power of 80%, 31 patients were needed with a hypothesis of improving ORR from 20% to 35%.

Results: Between October 2015 and June 2016, a total of 32 patients were enrolled in two referral institutes in Korea. Median age was 64 years (range 40-76) and 24 (75%) patients were male. All but one patient (97%) had metastatic or recurrent disease. Intrahepatic lesion is the most common primary tumor site (n = 13, 41%) and followed by gallbladder (n = 11, 34%) and extrahepatic lesion (n = 8, 25%). With median follow-up duration of 10.1 months, patients received median 12 cycles (range, 1-21) of study treatment. ORR was 50% as partial response was achieved in 16 patients. Median PFS was 7.1 months (95% CI, 5.3-8.8) and median OS was not reached. The 1-year PFS and OS rates were 25% and 59%, respectively. Most common grade 3-4 adverse events were neutropenia (n = 10, 32%), followed by diarrhea (n = 2, 6%) and peripheral neuropathy (n = 2, 6%).

Conclusions: OIS triplet combination chemotherapy was feasible and showed promising efficacy outcomes as first-line treatment in patients with advanced BTC. Randomized trial is needed to validate the efficacy of this triplet regimen.

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Legal entity responsible for the study: Hallym University Medical Center and Asan Medical Center

Funding: None

Disclosure: All authors have declared no conflicts of interest.

719P Prognostic impact of hepatitis B virus (HBV) infection in advanced intrahepatic cholangiocarcinoma (iCCA) patients (pts) treated with first-line gemcitabine plus cisplatin (GEMCIS)

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Background: HBV infection is a well-known risk factor of iCCA. However, its prognostic impact has rarely been investigated in pts with advanced iCCA who received chemotherapy.

Methods: Between April 2010 and May 2015, a total of 296 pts with histologically documented advanced iCCA received first-line GEMCIS in Asan Medical Center, Seoul, Korea, and were included in this retrospective analysis. Primary endpoint was overall survival (OS). In the multivariate analysis, variables which showed potential association with survival ($p < 0.15$) in the univariate analysis were included.

Results: Median age was 59 years (range, 27-78), and 62 (20.9%) pts with hepatitis B surface antigen positive formed the HBV group. Initially metastatic disease was the most common disease status at the time of GEMCIS (n = 184, 62.2%) followed by recurrence after curative surgery (n = 69, 23.3%) and locally advanced unresectable disease (n = 43, 14.5%). In comparison with the non-HBV group, HBV group were related with young age (mean age 56.4 vs 60.0), male predominance (74.2% vs 57.3%), lower rates of elevated CA 19-9 (42.0% vs 68.5%) and alkaline phosphatase (42.6% vs 60.5%) ($p < 0.05$ for all). In univariate analysis, HBV infection showed marginal relationship with poor OS (vs non-HBV infection; median 8.3 vs 10.0 months; HR = 1.27, p = 0.13). In multivariate analysis including potential prognostic factors, however, HBV group was significantly associated with poorer OS (HR = 1.52, p = 0.02). In addition, initially metastatic disease (vs locally advanced/recurrent disease; HR = 1.49), number of metastatic sites ≥2 (vs 0-1; HR = 1.50), poor ECOG performance status (2 vs 0-1; HR = 1.94), elevated total bilirubin (vs normal; HR = 1.83), and albumin <3.5 g/dL (vs ≥ 3.5 g/dL; HR = 1.53) were significantly associated with poorer OS ($p < 0.05$ for all).

Conclusions: Our results suggest that HBV infection might be an independent poor prognostic factor in pts with advanced iCCA treated with first-line GEMCIS. Further translational research is needed to define the differences in the molecular phenotypes between HBV- and non-HBV-associated iCCA.

Legal entity responsible for the study: Asan Medical Center, University of Ulsan College of Medicine

Funding: None

Disclosure: All authors have declared no conflicts of interest.

720P Inoperable carcinoma gallbladder: Comparison of two palliative chemotherapy regimens (gemcitabine-platinum versus CAPEOX)

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Background: Cancer of the gall bladder (CaGB) constitutes one of the ten commonest cancers in women in north India. Palliative chemotherapy is indicated for the advanced stage, inoperable patient in good performance status (PS). There is no standard-of-care regimen for this disease. We prospectively evaluated the efficacy & safety of GEMPLAT v/s CAPEOX chemotherapy in this cohort of patients.

Methods: Fifty chemo-naive, newly diagnosed patients (25 in each arm) of inoperable CA GB, in good PS (0, I, II) were included. Patients were randomised to receive either GEMPLAT or CAPOX. Primary end point was response rates (RR) & progression free survival (PFS); secondary end point: Overall survival (OS), toxicity & quality of life (QOL). Response assessment was done after every two cycles using by the RECIST 1.1 criteria. QOL was assessed every two cycles.

Results: Thirty one females & 19 males, mean age of 45.7 years (range 32 to 69) were included. There were no CRs in either arm. Partial response (PR) & stable disease (SD) was seen in 6 (24%) & 8 (32%) patients, respectively, in GEMPLAT arm; and 2 (8%) and 5 (20%) achieved PR and SD, respectively in CAPEOX group. Overall response rate (ORR) was 24% & 8%, respectively, for GEMPLAT & CAPOX. The median OS in GEMPLAT arm was 9.9 months versus 2.6 moths in CAPOX. The median PFS was higher in GEMPLAT group (7.6 months) as compared to CAPOX group (1.5 months). Grade 3/4 anemia & neutropenia occurred in 3 (12%) & 2 (8%) patients in the GEMPLAT arm, respectively with no grade 3/4 hematological toxicities in CAPOX arm. Five (20%) patients developed grade 3/4 transaminitis on GEMPLAT. One (4%) patients in CAPOX arm developed sensory neuropathy and 3 (12%) have grade 3/4 skin toxicity.

Conclusions: In our study, the GEMPLAT regimen showed higher RR, OS and PFS as compared to CAPOX. QOL was better in the GEMPLAT arm. CAPOX regimen was better tolerated and less toxic. The main toxicity of GEMPLAT was haematological & hepatic while that of CAPEOX was dermatological. We conclude that GEMPLAT should be the standard-of-care first line palliative chemotherapy regimen for inoperable CaGB patients in good PS. Larger, multi-centre studies are needed to confirm our findings and to compare CAPOX/other regimens with GEMPLAT.

Legal entity responsible for the study: Prof. Dr. Hemant Malhotra

Funding: None

Disclosure: All authors have declared no conflicts of interest.

721P Surgical indication for advanced intrahepatic cholangiocarcinoma according to the optimal preoperative carbohydrate antigen 19-9 cut-off value

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Background: The EASL guidelines for intrahepatic cholangiocarcinoma (ICC) discouraged resection for ICC patients with lymph node metastasis (LNM), intrahepatic metastasis (IM), or vascular invasion (VI). The clinical impact of hepatectomy in ICC patients with IM, periductal infiltration (MF+PI), LNM, and VI remains unclear.

Methods: Patients ICC who underwent hepatectomy for MF dominant ICC and unresected patients due to IM, LNM, or locally advanced tumors (unresectable group) were enrolled. The clinical impact of CA19-9 and hepatectomy were evaluated in ICC. The best CA19-9 cut-off value for ICC was examined based on the overall survival (OS). The surgical outcomes of patients who underwent hepatectomy for ICC with LNM, IM, VI, or PI were investigated, and survival of those patients was compared with that of patients with unresectable ICC based on their prognostic factors.

Results: A total of 73 resected patients and 20 unresectable patients were enrolled. The optimal CA19-9 cut-off value (based on the greatest difference in overall survival [OS]), was 300 U/mL. The OS at CA19-9<37 U/mL (n = 26; MST, 49.6 months) and 37-300 U/mL (n = 28; MST, 45.1 months) was comparable (P=0.842); however, the OS at CA19-9=37-300 U/mL was significantly better than that at CA19-9≥300 U/mL (n = 19; MST, 15.3 months; P<0.001). CA19-9≥300 U/mL, IM, and MF+PI were independent prognostic factors. Patients with CA19-9<300 U/mL who developed IM (MST, 35.2 months), MF+PI (MST, 32.9 months), LNM (MST, 34.0 months), VI (MST, 32.9 months) or who required major vascular resection (MST, 45.1 months) had a better prognosis than those with CA19-9≥300 U/mL who developed IM (MST, 8.7 months; P=0.001), MF+PI (MST, 7.5 months; P=0.040), LNM (MST, 8.7 months; P=0.005), or VI (MST, 8.7 months; P = 0.007), or who required major vascular resection (MST, 14.8 months; P=0.015); their prognosis was comparable to the unresectable group. (P=0.750, 0.767, 0.391, 0.224, 0.188)

Conclusions: Even if ICC patients develop IM, PI, LNM, or VI, or require major vascular resection, hepatectomy can be considered for selected patients with CA19-9<300 U/mL. However, surgeons should carefully determine the indications for resection in the patients with CA19-9≥300 U/mL.

Legal entity responsible for the study: Yusuke Yamamoto

Funding: None

Disclosure: All authors have declared no conflicts of interest.

722P A phase 2 study of lenvatinib monotherapy as second-line treatment in unresectable biliary tract cancer: Primary analysis results

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Background: Lenvatinib (LEN) inhibits vascular endothelial growth factor receptors, fibroblast growth factor receptors, and platelet-derived growth factor receptor-α. These targets have been shown to be expressed in patients (pts) with biliary tract cancer (BTC). A planned interim analysis of this phase 2 study demonstrated preliminary efficacy of LEN 24 mg/d in pts with BTC.

Methods: This open-label phase 2 study conducted in Japan enrolled pts aged ≥ 20 years with a confirmed unresectable BTC, measurable disease per Response Evaluation Criteria in Solid Tumors v1.1, and 1 prior gemcitabine (GEM)-based doublet chemotherapy to receive LEN 24 mg/d. The primary endpoint was objective response rate (ORR). Secondary objectives included disease control rate (DCR), overall survival (OS), progression-free survival (PFS), safety, and pharmacokinetics.

Results: The primary analysis was performed with data on 26 pts. Median age was 64 years and 15 pts (58%) were men. Eastern Cooperative Oncology Group performance status was 0 for 19 pts (73%) and 1 for 7 pts (27%). Six pts (23%) had prior surgery, 20 pts (77%) received prior GEM + cisplatin therapy, and 6 pts (23%) received prior GEM + TS-1. There were 6 pts (23%) with intrahepatic bile duct, 8 (31%) with extrahepatic bile duct, 10 (39%) with gallbladder, and 2 (8%) with ampulla of Vater primary tumor locations. ORR was 12% (90% CI: 3.2–27.2) by both independent and investigator review. DCR was 85% (90% CI, 68.2–94.6) by investigator, and 46% (90% CI, 29.2–63.8) by independent, review. Median PFS was 3.2 months (95% CI, 2.8–7.2) and 1.6 months (95% CI, 1.4–3.2) by investigator and independent review, respectively. Median OS was 7.4 months (95% CI, 4.5–11.3). All pts had treatment-emergent adverse events (TEAEs). Common TEAEs included hypertension, dysphonia, proteinuria, palmar-plantar erythrodysesthesia, decreased appetite, thrombocytopenia, and fatigue. TEAEs led to dose reduction in 20 pts (77%) and discontinuation in 2 pts (8%).

Conclusions: LEN 24 mg/d showed anti-tumor activity in pts with unresectable BTC who had failed GEM-based combination therapy. Toxicities were manageable with dose modifications, reductions, or discontinuations.

Clinical trial identification: NCT02579616

Legal entity responsible for the study: Eisai Inc

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Disclosure: M. Ikeda: Honoraria: Novartis, Bayer Yakuhin, BMS, Abbott Jpn, Eisai, Taiho, Ono, Kowa, Eli Lilly Jpn, Chugai, Nippon Kayaku, Daiichi-Sankyo, Yakult; Research: Bayer Yakuhin, Kyowa Hakko Kirin, Yakult, Taiho, Eli Lilly Jpn, Boehringer, Ono, Eisai, AZ. C. Morizane: Honoraria: Pfizer, Novartis, Yakult Honsha, Eli, Nobelpharma, FUJIFILM RI Pharm.; Consulting/advisory: AstraZeneca, Yakult Honsha, Novartis, Taiho Pharm.; Research funding: GSK, Pfizer, Nobelpharma, Eisai, Yakult Honsha, ONO Pharm, Taiho Pharm. N. Mizuno: Research funding: Zeria Pharmaceutical, Taiho Pharmaceutical, Merck Serono, AstraZeneca, NanoCarrier, Eisai, and MSD Honoraria: Taiho Pharmaceutical, Yakult Honsha, Novartis, Pfizer, and Kyowa-Hakko Kirin Speaker's bureau: Taiho Pharmaceutical. F. Nagashima: Honoraria: Sanofi, Chugai, Mitsubishi Tanabe, Taiho, Nestle; Research funding: Taiho, Daiichi-Sankyo, Sanofi, Eli Lilly, Sumitomo Dainippon, Eisai, MSD. S. Shimizu: Honoraria: TAIHO, Nippon Kayaku, Novartis. N. Hayata, H. Ikezawa, T. Suzuki: Employment: Eisai Co., Ltd. R. Nakajima: Stock or other ownership: Astellas Pharma, Chion Bioscience. C. Dutcus: Employment: Eisai Inc. M. Ueno: Research funding: ONO Pharma, Baxalta. All other authors have declared no conflicts of interest.

723P Genotyping and mRNA profiling reveal actionable targets in biliary tract cancers

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Background: Biliary tract cancer (BTC) is a heterogeneous disease of poor prognosis and variable pathogenesis, prompting for the identification of tumor features that may aid in the design of personalized treatments. Herein, we examined genotype and angiogenesis-related features in BTC.

Methods: We applied genotyping (Sanger, qPCR, 101-gene panel NGS) and mRNA relative quantification methods in 84 FFPE BTC (55 gallbladder [GBC], 14 intrahepatic [ICC], 15 extrahepatic [ECC] carcinomas), along with b-catenin immunohistochemistry (IHC).

Results: We identified 541 mutations in 68 (81%) tumors. Six GBC had 17 – 160 mutations, multiple per gene (hypermutated [hm]); non-hm tumors had <14 mutations. Top mutated genes were CTNNB1 (36%); PTEN (33%); TP53 (31%); PIK3R1 (29%); PIK3CA (13%); BRCA2 and KRAS (12%); BRCA1 (11%). In comparison to non-hm GBC, all hmGBC carried mutations in BRCA2 and other homologous recombination repair (HRR) genes, and also in PD1, but not in CTNNB1 and KRAS. None of the known pathogenic BRCA2 p.D2723G and BRCA1 p.Q563* and c.5266dupC was present at frequencies expected for germline mutations. We observed copy gains in EGFR (35% of tumors) and less frequently in PRKAR1A, PIK3CA, PIK3R1, MET and ERBB2. TP53 mutations were prevalent in GBC ($p < 0.001$) and PRKAR1A copy gains in ICC ($p = 0.007$). PTEN was co-mutated with CTNNB1 ($p < 0.001$). Unrelated to CTNNB1 mutations, nuclear b-catenin was detected in 45% of tumors, among them in 5/6 hmGBC. We observed strong mRNA expression correlation of the two neuropilins (NRP1 and NRP2) with each other (Spearman's rho 0.59) and with the endothelin receptor (EDNRA; NRP2 rho 0.66; NRP2 rho 0.51), as well as between VEGFA and its receptors (FLT1 rho 0.49; KDR rho 0.45). All PIK3CA mutated tumors expressed endothelin1 mRNA ($p = 0.010$). Most tumors expressing nuclear b-catenin were negative for VEGFC ($p = 0.009$) and FLT4 ($p = 0.002$) mRNA expression.

Conclusions: We confirmed the presence of different genotypes among GBC, ICC and ECC. Novel findings are the coexistence of PI3K and WNT pathway gene alterations in BTC, their association with angiogenesis, and the hmGBC subtype with HRR gene mutations, which may be considered for new treatment options in this difficult to treat disease.

Legal entity responsible for the study: Hellenic Cooperative Oncology Group (HeCOG)

Funding: HeCOG

Disclosure: G. Fountzilas: Honoraria: AstraZeneca. Consulting or advisory role: Pfizer, Sanofi, Roche Stock. Ownership: Ariad (immediate family member). All other authors have declared no conflicts of interest.

724P HER-2/HER-3 pathway as a potentially-actionable target in biliary tract cancers (BTCs): A retrospective analysis

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Background: Cholangiocarcinoma (CC), gallbladder cancer (GBC) and ampullary cancer (AC) (collectively BTCs) are poor-prognosis cancers. Cisplatin-gemcitabine chemotherapy is the standard treatment for patients (pts) with advanced BTC. New treatment targets are warranted; the human epidermal growth factor receptor (HER)-2 and HER-3 pathways may be potential candidates. High-quality data regarding expression and/or amplification rates in BTC are lacking.

Methods: Pts diagnosed with BTC and with available paraffin-embedded archival tissue were eligible. Seventy consecutive pts were required (power 0.91; assumptions: 5% (no expression) vs. 15% (expression of interest); α-error 0.1). All pts had been previously consented for tissue storage for research purposes. The study was approved by the local BioBank Ethics Committee. Overexpression of HER-2 and HER-3 was analysed by immunohistochemistry (IHC) following standard guidelines (gastric criteria were followed for HER-2); samples with "2+; borderline" IHC expression underwent additional fluorescence in-situ hybridisation (FISH). Kaplan Meier and Cox Regression analyses were employed for survival. Logistic regression was used to identify factors associated with HER overexpression.

Results: Of 167 screened pts between Jan-13 and Jul-15, 76 samples were retrieved for quality assessment; 67 were eligible with a median age of 65.6 years (range 32.9-79.3); 51.2% were female; 85.1% had ECOG performance status 0-1; all were adenocarcinomas. Primary site was GBC (n = 10, 14.9%), CC (n = 44, 65.7%; n = 26 intra-hepatic (ICC), n = 18 extra-hepatic (ECC)) and AC (n = 13, 19.4%). Stage at diagnosis: I/II (n = 21, 31.3%) or III/IV (n = 46, 68.7%). Estimated median overall survival (OS) for all pts was 15.9 months (95% CI 11.1-20.3). HER-2 overexpression was identified in 1 pt (1.5%). HER-3 overexpression was identified in 16 (23.9%): 1 pt was classified as "3+; positive" by IHC and 15 were confirmed by FISH following a "2+" expression in IHC. Neither HER-2 ($p = 0.103$) nor HER-3 ($p = 0.087$) impacted on OS. No factors related to HER-3 overexpression were identified.

Conclusions: HER-3 is overexpressed in a significant subset of pts diagnosed with BTC; treatment targeting this pathway may warrant evaluation.

Legal entity responsible for the study: MCRC Biobank

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Disclosure: All authors have declared no conflicts of interest.

725P Actionable molecular alterations in advanced biliary tract carcinomas: Preliminary data from the ProfiLER program (NCT01774409)

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Background: Patients (pts) with advanced biliary tract cancers (BTC) have poor prognosis and limited therapeutic option. The objectives were to characterize tumor genomic alterations for patients diagnosed with BTC enrolled in the ProfiLER program and identify actionable targets.

Methods: The ProfiLER program is a multicentric prospective molecular profiling trial in patients with advanced cancers. DNA extracted from either archival or freshly collected tumor samples was analyzed by targeted exon sequencing (NGS) of 59 cancer related genes and whole genome array comparative genomic hybridization (CGH). Genomic profiles were discussed at a dedicated molecular tumor board (MTB) for recommendation of molecularly targeted agents (MTA) when applicable.

Results: Of 2184 included pts in the ProfiLER program, 45 pts diagnosed with advanced BTC (intrahepatic cholangiocarcinoma – ICC, n = 32; vesicular carcinoma, n = 7; main biliary duct, n = 5; primary was unknown for one pt) were included between March 2013 to April 2017. Median age was 61 (range 35-78) years, and 21 pts (47%) were women. The median time from inclusion to MTB discussion was 12 (range 3-99) weeks. NGS was feasible for 31 pts (69%) and CGH for 24 (53%), both analyses were available for 22 (49%) and at least one analysis was available for 34 (75%) pts. 19 pts (56% of 34 analyzed pts) had at least one actionable alteration: *CDKN2A* homozygous deletion (n = 8), *MDM2* amplification (n = 3) and *PDGFRA* amplification (n = 5) were the only recurrent alterations. Among 31 pts with NGS data, 7 had TP53 mutations, 4 had KRAS mutations while none had BRAF mutations. Four pts received MTA based on the alteration identified (CDK4/6 inhibitor for CDK4 amplification, ERBB2 inhibitor for a ERBB2 mutation, EGFR inhibitor for EGFR mutation and mTOR inhibitor for homozygous TSC2 deletion), progressive disease was the best response in all pts.

Conclusions: CGH and NGS identified actionable alterations in 56% of pts with BTC for whom analyses could be performed. However, the analyses were both feasible in only 49% of patients due to the use of archival biopsy samples in most cases.

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Legal entity responsible for the study: Centre Léon Bérard

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726P Precision medicine for patients with advanced biliary tract cancers: Updated results from the prospective MOSCATO trial

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Background: Advanced biliary tract cancers (aBTCs) are heterogeneous diseases with a median overall survival (OS) < 1year. Platinum-based chemotherapy doublets are the frontline standard-of-care. Increasing evidence points out the strong addiction of aBTCs to druggable oncogenic alterations. We assessed the success rate and the clinical benefit of administering molecular targeted agents (MTAs) based on the molecular alterations found in patients with aBTCs.

Methods: Patients with aBTCs were prospectively enrolled in our prospective molecular screening program (MOSCATO 01). An on-purpose tumor biopsy was performed for each patient, followed by high-throughput molecular analysis. Patients were then guided to MTAs matching the molecular alterations. The primary endpoint was progression-free survival (PFS), with clinical benefit defined by a PFS ratio (PFS [MTA]/PFS [prior line]) >1.3.

Results: From November 2011 to March 2016, among 1036 adult patients included in the MOSCATO-01 trial, 48 biopsy procedures were performed in 43 patients (4%) with aBTC (4 patients re-included, one 3 times).Thirty three patients (77%) had intrahepatic cholangiocarcinoma. Patients had failed a median of 2 previous lines (range, 1-5). Successful biopsy procedures and DNA extractions enabled molecular analysis in 38 samples (79%), and at least one molecular alteration was detected in 35 samples (71%). Following analysis, 25 patients could be orientated to an appropriate early clinical trial or accessible MTA (25/38, 66%), and 19 patients could be treated on the basis of molecular alterations (19/38, 50%). For the biology-driven treatment group, The PFS ratio was 1.52 [0.08, 7.1]. Six patients (32%) had an objective response (complete [CR] or partial [PR] response), 16 (84%) had a clinical benefit (stable disease+PR+CR), and 7 (37%) had a PFS≥6 months. This strategy led to a significant overall survival improvement compared to patients who were not treated according to their tumor molecular characterization (HR = 0.26 [95%CI, 0.10 − 0.67], p = 0.003).

Conclusions: With 25 patients out of 48 inclusions (52%) driven to a MTA, patients with aBTCs are ideal candidates for molecular profiling.

Clinical trial identification: MOSCATO (NCT01566019)

Legal entity responsible for the study: Jean Charles Soria

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727P Preoperative chemoradiotherapy after induction FOLFIRINOX improve R0 resection margins rate and histological response in patients secondary resected in borderline or locally advanced pancreatic adenocarcinoma

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Background: Previous studies have shown increased survivals in patients (pts) with borderline (BR) or locally advanced (LA) pancreatic adenocarcinoma (PAC) resected after induction FOLFIRINOX (i-FLX). Two-thirds of pts received also chemoradiotherapy (CRT) in most series. The aim of this study was to evaluate the impact of preoperative CRT after i-FLX in pts resected for BR or LA PAC.

Methods: Data of pts who underwent a curative intent resection after i-FLX with or without concomitant fluoropyrimidine- or gemcitabine-based CRT in 23 French centers from AGEO/FRENCH groups were reviewed in this retrospective study.

Results: From November 2010 to December 2015, 203 pts (119 men, median age of 61.7 years, 106 BR and 97 LA) underwent a pancreatic resection after a median number of 6 cycles (1-30) of i-FLX. CRT was administered in 102 pts (50%), 49 (46%) BR and 53 (54%) LA, with 54 Gy (45-59) median of radiation dose. Initial median tumour size was 31.5 mm (10-110), 82.3% located in the pancreatic head. 40% (n = 80) of tumours required vascular resection. Post-operative mortality (D-60) and morbidities (grade 3-4) were 3.4% and 19.7%, respectively. R0 resection was achieved in 83.3% (n = 169) of pts, higher in those receiving CRT (89.2% vs. 76.2%; p = 0.01). The histological complete response (ypT0N0) and major response (ypT0-1N0) rates were 11% (n = 22) and 23% (n = 47) respectively, significantly higher in pts with CRT (16.0% vs. 5.1%;

p = 0.009 and 32.0% vs. 13.4%; p = 0.001). After a median follow-up of 34.4 months, recurrence occurred in 118 pts (58.1%) and 76 (37.4%) died. Median DFS and OS were 16.7 [95% CI: 12.7-20.7] and 46.7 months [95% CI: 37.7-55.7] respectively. Pts receiving additional CRT had longer disease free survival (19.0 vs. 13.3 months; p = 0.17) and significantly longer overall survival than those receiving i-FLX alone (62.9 vs. 35.0 months; p = 0.028).

Conclusions: In this retrospective study, preoperative CRT after i-FLX seems to improve R0 resection rates and histological responses in pts resected for BR or LA PAC. Surgery after i-FLX seems to be safe even when combined with CRT. This strategy should be further evaluated in a prospective manner.

Legal entity responsible for the study: Dr. Daniel Pietrasz

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728P Intratumoral heterogeneity of SMAD4 immunohistochemical (IHC) expression and its role in prediction of recurrence patterns in patients with resectable pancreatic cancer (PC)

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Background: Up to 30% of patients with resectable PC have only locoregional recurrences and never experience metastatic disease. Several authors reported SMAD4 expression can predict locoregional pattern of PC progression. The aim of our study was to evaluate consistency of SMAD4 expression in different tumor areas and its correlation with patterns of PC recurrence.

Methods: Records of PC patients treated in N.N. Blokhin Russian Cancer Research Center since 2002 to 2015 were analyzed. Inclusion criteria for this retrospective analysis were: nonmetastatic morphologically confirmed PC, R0-R1 resection and archive tumor samples availability. Formalin-fixed, paraffin-embedded tissue sections of different areas of the primary tumor (central area and zones of invasion) and of lymph node metastases were analyzed via IHC for SMAD4 expression using TMA technology.

Results: A total of 356 tissue sections obtained from 91 patients were assessed for SMAD4 expression. Positive SMAD4 expression was revealed in tumor blocks of 26 patients. There was high intratumoral heterogeneity of SMAD4 expression: only in 4 of 26 patients (15.4%) SMAD4 expression was positive in all assessed tumor slides. There were 54 recurrences (9 locoregional, 41 distant and 4 both local and distant) with median follow-up 21.7 months. There were no correlation between SMAD4 expression and locoregional recurrence pattern (Goodman & Kruskal's tau coefficient 0.08 ± 0.03, p = 0,13). There was no difference in distant recurrence-free survival by SMAD4 IHC expression status: medians were 11.8, 19.5 and 7.1 months for patients with SMAD4 negative, heterogeneous or positive tumors, respectively (p = 0.987). SAMD4 status also showed no prognostic significance: medians overall survival were 20.5, 32.6 and 15.2 months for patients with SMAD4-positive, heterogeneous and negative tumors, respectively (p = 0.131).

Conclusions: Different areas inside the primary tumor and lymph node metastases heterogeneously express SMAD4. SMAD4 IHC expression is not a biomarker of a recurrence pattern following surgical resection for PC.

Legal entity responsible for the study: N.N. Blokhin Russian Cancer Research Center

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Disclosure: All authors have declared no conflicts of interest.

729P Outcome of patients with pancreatic adenocarcinoma with complete pathological response following neo-adjuvant therapy

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Background: Recently, the natural history of metastatic pancreatic adenocarcinoma (PC) has changed after the introduction of new chemotherapeutical regimens FOLFIRINOX and gemcitabine/nab-paclitaxel, with median overall survival exceeding the year. These regimens were also largely prescribed in the neo-adjuvant setting for locally advanced (LAPC) and borderline (BPC) PC leading sometimes to a complete pathological response (CPR) rarely seen with previous neoadjuvant regimens. The aim of this study was to assess outcomes of patients (pts) who presented CPR after induction therapy for PC.

Methods: We retrospectively identified pts with PC presenting CPR after neo-adjuvant therapy in 7 participating French centers from the AGEO group between November 2010 and March 2017.

Results: 26 pts were enrolled, 12 had LAPC, 13 BPC and 1 oligo-metastatic PC; M/F ratio was 1.6 and mean age was 61 years. All pts were treated with neo-adjuvant FOLFIRINOX (n = 26), de-escalated to gemcitabine (n = 1) and FOLFIRI (n = 2). The median number of cycles was 6 [4-24] and 85% of pts received neo-adjuvant radiation therapy after chemotherapy. Response to neo-adjuvant chemotherapy (RECIST V1.1), was as follow: CR 8% PR 57%, SD 27% and 8% were not evaluated. 30% of pts received adjuvant chemotherapy mainly with gemcitabine and 9 (35%) relapsed (distant metastases, n = 8). Median time to recurrence in pts that replapsed was 12.9 months. After a median follow-up of 29.5 months, the median overall survival (OS) from surgery was not reached and the median disease free survival was 38.8 months. The 1-year and 2-year OS rates were respectively 100% and 94%. The 1-year and 2-year DFS rates were 86% and 70%.

Conclusions: CPR seem to be an important prognostic marker in pts resected of a PC after neo-adjuvant therapy. The limited recurrences rate and the 1 and 2-year OS and DFS rates are very promising. A longer follow-up and prospective series are now necessary to confirm the favorable outcomes of these PC with CPR.

Legal entity responsible for the study: AGEO French Study Group

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730P Interim health related quality of life (QoL) from LAPACT, a Phase 2 trial of nab-paclitaxel (nab-P) plus gemcitabine (G) for patients (Pts) with locally advanced pancreatic cancer (LAPC)

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Background: Disease burden and cumulative toxicity due to chemotherapy may negatively impact QoL of pts with cancer. Early results from the LAPACT trial suggest promising efficacy of *nab*-P + G in LAPC. An evaluation of the potential impact of *nab*-P + G on health-related QoL is warranted.

Methods: During induction, treatment-naive pts with unresectable LAPC and ECOG PS ≤ 1 received 6 cycles (C) of *nab*-P 125 mg/m^2 + G 1000 mg/m^2 D 1, 8, and 15 of each 28-day C. After induction, pts without PD or unacceptable AEs were eligible for the investigator's choice (IC) of continued treatment (Tx) with *nab*-P + G, chemoradiation, or surgery. Surgery could occur prior to completing 6 C if the investigator deemed a sufficient tumor response. Pt-reported QoL, a secondary endpoint, was assessed via EORTC QLQ-C30 and QLQ-PAN26 at initial screening, during the induction and IC phases on D 1 of each C, and at follow-up after the last dose. Results presented here are from the induction phase. Data for pts receiving their first Tx dose by Oct 1, 2016 are reported.

Results: A total of 101 pts received Tx, and 75% (76/101) pts had a baseline and ≥ 1 postbaseline QoL assessment. The median age was 65 years (range, 42-85); 53% had an ECOG PS 1. All QoL dimensions were improved/stable in ≥ 67% of pts (Table). In general, median time to improvement was ≤ 1 week of completing the first Tx C (28 days/C). A majority (> 60%) of pts had ≥ 1 complete resolution of anxiety (tense), constipation, depression, nausea, or pain during induction. Forty-two percent of pts received additional Tx during the IC phase.

Conclusions: QoL was generally improved/stable during induction, with some dimensions improving within 1 week of completing the first C. This suggests that QoL is

Table: 730P Stability, Improvement, and Resolution in the EORTC-QLQ C30

Dimension[a]	Stable or Improved, %[b] (n = 76 evaluable)	Median Time to Improvement, days	Complete Resolution at Least Once, n/n[b] (%)
Anxiety			
Tense	90.8	32.0	34/54 (63.0)
Worry	86.8	31.5	29/63 (46.0)
Constipation	88.2	29.0	28/39 (71.8)
Depression	85.5	29.0	21/32 (65.6)
Difficulty remembering things	86.8	32.0	14/25 (56.0)
Fatigue	76.3	30.0	10/63 (15.9)
Insomnia	85.5	34.0	28/55 (50.9)
Irritability	86.8	31.5	20/40 (50.0)
Lacked appetite	85.5	33.0	30/52 (57.7)
Limited in pursuing hobbies or leisure	77.6	34.5	13/37 (35.1)
Limited in work or other daily activity	82.9	30.0	13/38 (34.2)
Nausea	88.2	50.0	22/28 (78.6)
Need to rest	81.6	33.0	7/58 (12.1)
Need to stay in bed or chair during day	85.5	51.0	15/33 (45.5)
Pain	90.8	29.0	36/59 (61.0)
Pain interfering with daily activity	90.8	30.0	26/39 (66.7)
Physical condition or medical treatment			
Caused financial difficulties	90.8	35.0	12/25 (48.0)
Interfered with family life	76.3	37.0	17/31 (54.8)
Interfered with social activities	81.6	52.0	16/42 (38.1)
Trouble doing strenuous activity	81.6	29.5	4/40 (10.0)
Trouble taking long walks	77.6	30.0	7/45 (15.6)
Weakness	67.1	30.0	14/53 (26.4)
Overall health	75.0	33.0	not applicable

[a]Dimensions included were those experienced by ≥ 25 pts at baseline and evaluable at ≥ 1 postbaseline assessment. All were measured during induction phase.
[b]Pts who had ≥ 1 complete resolution of the limitation/pts who experienced the limitation.

preserved or improved with *nab*-P + G and indicates that the regimen was active and tolerable, with a majority of pts completing induction without PD. NCT02301143.

Clinical trial identification: NCT02301143

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731P Prognosis of familial pancreatic cancer (FPC): A matched case analysis

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Background: FPC is a putative genetically heterogeneous syndrome defined as kindreds with multiple blood relatives with pancreatic adenocarcioma (PDAC). It has been hypothesized that germline mutations in DNA repair genes contribute to FPC, resulting in variable outcomes and response. We evaluated survival in FPC patients (pts) with resectable and unresectable PDAC.

Methods: Pts were identified from the Ontario Pancreatic Cancer Study database, recruited from January 1998-July 2016. All pts were seen by genetic services. FPC pts were age and stage matched with cases without a family history of PDAC and who tested germline BRCA mutation negative (non-FPC). Stage was classified as early operable (I/II) or late inoperable (III/IV). Pts were matched within 5 years of the treatment period. Only those who had either received surgery or at least 1 cycle of chemotherapy were included. The Kaplan-Meier method was used to assess survival.

Results: 144 pts were evaluated, 72 in each cohort. In the FPC group, 65 pts had at least 1 FDR with PDAC and 7 pts, at least 2 relatives (1^{st}-3^{rd} degree) with PDAC. Median age was 66 years; there were more females in the FPC group (54% vs 49%). 33 pts (46%) in each group had early stage disease and received surgery. Adjuvant therapy was given in 70% and 73% of the FPC and non-FPC cohorts respectively. 1 FPC pt, received adjuvant gemcitabine/erlotinib. 6 non-FPC pts received FOLFIRINOX, 3 as neo-adjuvant and 3 as adjuvant treatment. Of those with late stage disease, (n = 39 each), combination chemotherapy was given in 23 (59%) and 28 (72%) pts in FPC *vs* non-FPC groups respectively. The median overall survival (OS) was 16 months (mths) in the FPC group *vs* 13mths in the non-FPC group (p = 0.46). Stratifying by stage, in FPC vs non-FPC pts, median OS in early disease was 31 *vs* 27 mths (p = 0.73) and in late disease 13 vs 9 mths (p = 0.12). Platinum was used in 18 (46%) FPC and 17 (44%) non-FPC pts with late disease. Platinum regimens improved median OS overall compared to no platinum (12mths vs 9mths, p = 0.04) but was not associated with FPC status.

Conclusions: FPC is poorly understood but trends towards a better prognosis and response to therapy. The use of platinum based chemotherapy in these pts could be considered; however further research is warranted.

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Disclosure: All authors have declared no conflicts of interest.

732P Should pancreatic cancer be included in BRCA1/2 testing criteria?

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Background: BRCA1/2 mutation carriers have an increased risk for breast cancer (BC), ovarian cancer (OC), prostate cancer and pancreatic cancer (PC). On this basis, the NCCN Guidelines include prostate and PC among the BRCA testing criteria. In our Institution, BRCA diagnostic test is exclusively offered to patients affected by BC or OC, according to the Modena criteria, or to healthy women with BRCAPro> 40%. The aim of this study was to compare the rate of positive BRCA test in families with PC, classified according to NCCN guidelines or Modena criteria.

Methods: We retrospectively analyzed families with family history of PC registered in the archive of our Family Cancer Clinic. Analysis of BRCA1/2 mutation was evaluated in these families and the BRCA mutation detection rate was calculated according to both selection criteria. We also evaluated age at diagnosis and overall survival of patients affected by PC.

Results: 435 families with at least one diagnosis of PC have been identified. 393 families had PC and BC and/or OC cases and were included in our analysis. 55.5% of these families were candidate to BRCA testing according to the Modena Criteria, whereas 90.8% of families were candidate according to the NCCN Guidelines. 65.6% of families selected according with the Modena Criteria underwent BRCA test, identifying 19 BRCA1 mutations and 16 BRCA2 mutations (detection rate 24.5%). 45.9% of families with the NCCN Criteria underwent the test with the identification of the same mutations (detection rate 21.3%). Mean age at PC diagnosis was lower in patients with family history of BC and/or OC (65.8 years) and in BRCA mutated families (65.7 years) than in general population (72 years). One-year OS rate was higher in patients with family history of BC and/or OC (41.3%) and in BRCA mutated families (50%) than in general population (23%). 5-year OS was around 5% for patients with family history or BRCA mutation in the family and general population.

Conclusions: Our retrospective study confirms the high rate of positive BRCA1/2 test in families with PC associated to BC and/or OC. The NCCN Guidelines compared to the Modena Criteria did not increase the BRCA mutation detection rate. Notably, PC diagnosed in families with history of BC and/or OC or BRCA mutation showed younger age at diagnosis and better 1-year OS. We are planning to test all the remaining families selected by NCCN guidelines.

Legal entity responsible for the study: Dr. Laura Cortesi

Funding: None

Disclosure: All authors have declared no conflicts of interest.

733P Sequential chemo-chemoradiation (CCRT) in locally advanced pancreas cancer in an irish high volume centre

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Background: We adopted the sequential CCRT approach for management of patients (pts) with LAPC in July 2008. Pancreas cancer care was centralised to 2 high volume cancer centres in Ireland since 2011. The objective of this study is to examine the efficacy of CCRT and its differences pre- and post-July 2008, and to compare the efficacy of newer chemo-regimens FOLFIRINOX (FFX) and Gemcitabine/nab-Paclitaxel (GA) with other regimens.

Methods: Pts were identified from the medical oncology and pancreatobiliary surgery databases. Eligible pts had pathological diagnosis of pancreatic adenocarcinoma, and radiologically and/or laparoscopically-confirmed LAPC disease with no distant metastases. Only those who commenced induction chemo were included in the final analysis. OS was calculated from date of pathological diagnosis to death.

Results: Between Mar 05 - Apr 17, 102 pts were identified. 56, 55% were male with a median age of 67 yrs (range: 42 – 87). 86 pts commenced induction chemo, with FFX+GA (15 + 5), gemcitabine (30), gemcitabine-based (24) and fluorouracil-based regimen (12). All pre-July 08 pts were treated with chemo only. Post-July 08, 70 pts commenced induction chemo, and 38, 54% went on to have sequential CRT (s-CRT). Those who received combination chemo were more likely to proceed with s-CRT, 84% vs 59% respectively, p = 0.023. 5FU was the most common radiosensitiser used (20), followed by gemcitabine (5). Median follow-up was 12.5 mos (95% CI: 11.60 -15.34). OS for all 86 pts were 13.4 mos (95% CI: 11.8- 15.0) and for post-July 08 cohort was significantly longer (14.1 mos vs 8.9 mos, HR: 0.47, 95% CI 0.26 – 0.83, p = 0.01). Amongst the post-July 08 pts, OS for patients who received s-CRT was significantly superior when compared to patients who did not (18.1 vs 10.0 mos, HR 0.35, 95% CI 0.21 – 0.58, p < 0.001). Induction chemo with FFX/GA showed numerical improvement in OS, 16.9 vs 13.3 mos, HR 0.83, 95% CI 0.48 – 1.43, p = 0.5). 6 pts went on to have resection and all were post-July 08 cohort (OS: 18.1 vs 13.3 mos, p = 0.4).

Conclusions: Our results showed superior OS for pts who received CCRT since the implementation of CCRT and centralisation of pancreas cancer care. Treatment with newer regimen appear to improve OS.

Legal entity responsible for the study: St. Vincent's University Hospital, Dublin, Ireland.

Funding: None

Disclosure: All authors have declared no conflicts of interest.

735P The prognostic significance of infiltrating lymphocytes in resectable pancreatic ductal adenocarcinoma in untreated versus neoadjuvant treated patients

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Background: Tumor microenvironment plays an important role in chemoresistance and tumor progression of PDAC. The role of tumor infiltrating lymphocytes in treated PDAC remains unclear. This study examines the distribution of intratumoral lymphocytes and their correlation with survival and clinicopathologic factors in patients with resected PDAC.

Methods: We studied 75 patients who completed pancreaticoduodenectomy (PD) plus neoadjuvant therapies between 1999 and 2007. Neoadjuvant therapies included Gemcitabine + nab-paclitaxel and FOLFIRINOX or chemoradiation. Immunohistochemistry (IHC) for CD4, CD8, and FOXP3 were performed on resection specimens, which contained two representative slides from each patient. Digital images of IHC-stained slides were obtained at 20 x magnifications using a whole slide scanner (ScanScope, Aperio AT Turbo). Tumor regions were hand-annotated on whole slide images and computer assisted quantitative analysis was performed using Aperio's ImageScope software. The tumor infiltrating lymphocytes were calculated as the percentage of positive staining area vs the total tumor area. Cox Regression analysis was performed for univariate and multivariate analysis.

Results: The average percentage for CD4, CD8 positive cells were 6.08 ± 7.76, 2.84± 3.64, respectively in the treated cohort. Using the 50 percentile value as a cutoff, patients with high CD4+ lymphocytes had better disease free survival vs low CD4 positive lymphocytes (HR 0.234, P = 0.0031). There were no significant correlations between CD 4+, CD8+, CD68+, Granzyme B+, KP-1+, FOXP3+ lymphocytes and overall survival (p > 0.05). In multivariate analysis, neither CD4+ lymphocytes (HR: 0.49, P = 0.004), CD 8+ or CD 4/CD 8 ratio were independent prognostic factors for overall survival (See table).

Conclusions: Our study showed that the presence of high CD4+ and CD8+ lymphocytes is an independent prognostic factor for disease free survival in resectable neoadjuvant treated PDAC patients. We believe that neoadjuvant chemotherapy induces an enhanced immune response that may contribute to improved survival outcomes. Results are currently being analyzed looking at tumor infiltrating lymphocytes in resectable PDAC patients receiving receiving surgery alone.

Table: 735P

Variable	Univariate Analysis (DFS)		Mulitivariate Analysis (DFS)	
	P-value	HR (95% CI)	*P*-value	HR (95% CI)
CD 4 High vs. Low (Reference)	0.003	0.234 (0.073-0.627)	0.510	0.553 (0.094-3.220)
CD 8 High vs. Low (Reference)	0.021	0.366 (0.146-0.858)	0.695	0.752 (0.170-2.919)
CD 4/CD 8 ratio High vs. Low (Reference)	0.046	0.393 (0.141-0.983)	0.112	0.344 (0.084-1.281)
CD 68/CD 4 ratio High vs. Low (Reference)	0.085	0.424 (0.123-1.114)	0.261	0.521 (0.135-1.561)

Legal entity responsible for the study: MD Anderson Cancer Center
Funding: None
Disclosure: All authors have declared no conflicts of interest.

736P Randomized phase 2 trial of peri- or post-operative chemotherapy in resectable pancreatic adenocarcinoma

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Background: Pancreatic ductal adenocarcinoma (PDAC) has a remarkable trend to metastasize early. Accordingly, there is a strong rational to investigate preoperative chemotherapy in patients with resectable disease. We conducted a multicenter randomized phase 2 trial (PACT-15; NCT01150630) to assess the role of combination chemotherapy in perioperative setting.

Methods: Treatment-naïve patients with 18-75 yr, KPS>60 and pathologically confirmed stage 1-2 resectable PDAC were randomized to surgery followed by 6 cycles of adjuvant gemcitabine 1000 mg/m^{2}1,8,15q4w (arm A), or PEXG (cisplatin 30 mg/m^2, epirubicin 30 mg/m^2, and gemcitabine 800 mg/m^2 1,15q4w and capecitabine 1250 mg/m^2/day 1-28) (arm B), or to 3 cycles of PEXG before and 3 after surgery (arm C). The primary endpoint was 1-year event-free survival (EFS); the secondary endpoints were EFS, overall survival (OS), and the difference in pathological findings between arm A+B and arm C. With 24 eligible patients in each group (H0 20%, H1 40%, α 10%, β 20%), $\leq$16 events of 24 would support further evaluation of experimental therapy.

Results: Between September 2010 and April 2015, 88 eligible patients were randomized in 9 Italian centers (arm A: 26, B: 30, C: 32). Basal patients and tumor characteristics were well balanced across arms. One-year EFS (A, B, C) was 6/26 (23%), 15/30 (50%), 23/32 (72%). Median EFS was 4.8, 12.4, 18.9 months (A vs C p=0.002). Three-year OS (A,B,C) was 35%, 42%, 55%. Median OS (A,B,C) was 20.4, 25.1, not reached at 33 months (A vs C p = 0.022). Pathological results are summarized in the table. Treatment safety profile was good.

Table: 736P Pathological findings

	A+B	C
Enrolled	56	32
T resection	49 (88%)	27 (84%)
Intraoperative metasteses	7/56 (13%)	2/32 (6%)
Postoperative metastases	10/56 (18%)	3/32 (9%)
Grade 3	29/49 (59%)	6/27 (22%)
T1	2/49 (4%)	4/27 (15%)
No	13/49 (27%)	13/27 (48%)
Ro	16/49 (33%)	15/27 (56%)
Median size	2.5 cm	2.0 cm

Conclusions: Patients receiving perioperative chemotherapy had significant improvement of EFS and OS as compared to those receiving adjuvant treatment. This trial provides the strongest piece of evidence currently available in favor of preoperative chemotherapy in resectable PDAC.

Clinical trial identification: NCT01150630
Legal entity responsible for the study: IRCCS San Raffaele Scientific Institute, Milan, Italy
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737P TP53 mutation predicts sensitivity to adjuvant gemcitabine in pancreatic cancer: Results from the CONKO-001 study

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Background: Pancreatic adenocarcinoma (PDAC) is a molecular heterogeneous disease, but clinically relevant genetic biomarkers are still missing. There are no data from prospective studies after curatively intended surgery and adjuvant chemotherapy so far.

Methods: CONKO-001, was a prospective randomized phase III study and investigated the role of adjuvant gemcitabine (Gem) as compared to observation (Obs). Formaline-fixed paraffin-embedded tissue samples of 187 patients (pts) could be collected, of which 97 could be analysed after DNA-extraction by targeted next generation sequencing (NGS), using a predefined sequencing panel including mutation hotspot regions of 36 genes (ACTN4, ACVR1B, APC, ARID1A, ARID1B, ARID2, ATM, BRAF, CDK6, CDKN2A, CNDP2, CREBBP, CTNNB1, ERBB2, FGFR1, GATA6, KDM6A, KMT2C, KMT2D, KRAS, MAP2K4, MET, MYC. PBRM1, PIK3CA, PREX2, RNF43, RPA1, SF3B1, SMAD4, SMARCA2, SMARCA4, SOX9, STK11, TGFBR2, TP53). Mutational status was correlated with survival by fitting a cox proportional hazard model.

Results: Patient's characteristics were balanced between Gem (n = 49) and Obs (n = 48) group. KRAS, TP53, SMAD4 mutation was found in 73% (Gem/Obs n = 33/38), 59% (n = 28/29), 8% (n = 4/4) of patients. KRAS/SMAD4 mutation status was not associated with (treatment-related) survival. TP53 mutation was identified as a negative prognostic factor for untreated patients: hazard ratio (HR) for disease free-survival (DFS) TP53 mutant vs TP53 wildtype 2.90 (95% CI 1.55 -5.41). Furthermore, TP53 mutation was found to be a positive predictive factor for Gem: HR for DFS Gem vs Obs in TP53 wildtype patients was 0.87 (95% CI 0.46-1.66) in comparison to TP53 mutated patients with a HR of 0.22 (95% CI 0.12-0.39). Test of TP53-by-treatment-interaction was statistically significant; p = 0.002.

Conclusions: To the best of our knowledge, we present the first NGS data from a prospective clinical study in PDAC. In contrast to previous data, we could not identify KRAS or SMAD4 mutation as clinically relevant factors in primarily resectable PDAC. In CONKO-001, TP53 mutated patients had an unfavorable prognosis when randomized to Obs and profited strongly from adjuvant Gem, while adjuvant treatment did not significantly prolong DFS in TP53 wildtype patients.

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Legal entity responsible for the study: Charite Universitätsmedizin Berlin, CONKO-study group.
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738P Strong tumour cytidine deaminase (CDA) staining predicts for improved survival associated with sequential nab-Paclitaxel (nabP) and gemcitabine (GEM) chemotherapy as first line treatment of patients (pts) with metastatic pancreatic adenocarcinoma (mPDAC)

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Background: *Nab*P+GEM chemotherapy improves survival as treatment for mPDAC, compared with GEM alone. The UK randomised phase 2 SIEGE trial showed that sequential (SEQ) delivery of *nab*P+GEM (with *nab*P given 24 hours before GEM) trended towards improved efficacy compared with standard concomitant (CON) delivery. Preclinical models suggest that *nab*P potentiates GEM activity by either impacting on stroma or reducing CDA levels.

Methods: 146 pts were randomised to receive CON or SEQ *nab*P+GEM. Baseline whole blood (wb) CDA activity was measured using an endpoint read, spectrometric, plate based assay. Baseline tumour IHC assessed stromal content (H&E), CDA (ab137605) and nucleoside transporter protein, hENT1 (Ventana SP120) expression.

Results: 6-month (m) progression-free survival (PFS, primary end point) by SEQ and CON arms was 47% and 33%; median PFS was 5.8 and 4.1m (HR 0.68, 95%CI 0.48-0.97); median overall survival (OS) was 10.1 and 7.9m, respectively. Baseline wb CDA activity correlated only with ANC (R^2 0.70, p<.0001) after adjustment for other baseline factors

including KPS, disease burden, CRP and did not predict for PFS, OS or toxicity. Of 105 tumours evaluable by IHC, 34 had diffuse strong (ds) CDA staining which predicted for improved PFS with SEQ therapy (HR 0.43, 95%CI 0.20-0.91); this was not evident for other staining patterns or ds-CDA staining for pts on CON therapy. Ds-CDA staining trended towards improved OS with SEQ compared with CON therapy (HR 0.73, 95%CI 0.35-1.52). On disease progression, 34 pts (13 SEQ, 21 CON) received further anti-cancer treatment. Stroma or hENT1 expression did not predict for PFS or OS with SEQ or CON therapy. Tumour stroma staining, but not CDA or hENT1, was an independent prognostic factor for improved OS (moderate/extensive vs none/little, HR 0.55, 95%CI 0.37-0.84).

Conclusions: Whole blood CDA activity was not a useful predictive biomarker, due to the dominant neutrophil effect. Instead, strong tumour CDA expression predicted for pts most likely to have a survival benefit from SEQ therapy and warrants further exploration.

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Legal entity responsible for the study: Cambridge University Hospitals NHS Foundation Trust

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739P Randomized phase 2 trial of nab-paclitaxel plus gemcitabine, ± capecitabine, cisplatin (PAXG regimen) in metastatic pancreatic adenocarcinoma

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Background: The recommended phase 2 dose of *nab*-paclitaxel (150 mg/m^2) in combination with cisplatin, capecitabine, and gemcitabine (800, 30, and 1250 mg/m^2 every 2 weeks, respectively; PAXG regimen) were determined in a phase Ib trial. We now report the final results of a randomized phase 2 trial of PAXG or nab-paclitaxel-gemcitabine (AG) in metastatic pancreatic adenocarcinoma (NCT01730222).

Methods: Previously untreated patients with pathologic diagnosis of metastatic pancreatic adenocarcinoma, 18-75 years, Karnofsky Performance Status $\geq$ 70 were eligible. Primary endpoint was the progression-free survival rate at 6 months (PFS6). With 42 eligible patients in each group, a PFS6 in $\geq$ 25 of 42 would support further evaluation of the PAXG regimen.

Results: Between Apr 2014 and June 2016, 83 patients (table 1) were randomized at a single Institution to receive PAXG (arm A; N = 42) or AG (arm B; N = 41). PFS6 was 31/42 (74%), and 24/41 (59%), respectively. PFS at 1 year and median PFS was 26% and 8.1 for arm A and 7% and 6.8 months for arm B. One-year survival was 62% and 41%, respectively. Median survival was not reached at 13.5 months for arm A and was 11.2 for arm B. PAXG regimen did not increase grade 3-4 extra-hematological toxicity as compared to AG.

Table: 739P Baseline Characteristic

		PAXG	AG
Number		42	41
Male/female		20/22	23/18
KPS	90-100	34 (81%)	26 (63%)
	70-80	8 (19%)	15 (37%)
Age	median	66	63
	range	44-75	29-75
Biliary stent		9 (22%)	8 (19%)
CA19.9	>ULN	32 (76%)	31 (76%)
	median	1413	1546
Neutrophil/Lymphocyte >5		15%	21%

Conclusions: The results show that addition of cisplatin and capecitabine to the AG backbone is feasible and linked with improved disease control. The PAXG regimen warrants further exploration in this setting of patients.

Clinical trial identification: NCT01730222

Legal entity responsible for the study: IRCCS San Raffaele Scientific Institute, Milan, Italy

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740P The impact of UGT1A1 genetic polymorphism on safety in unresectable pancreatic cancer patients receiving FOLFIRINOX therapy: A subset analysis of JASPAC 06 study

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Background: UGT1A1*6 and UGT1A1*28 polymorphisms were reported to be associated with increased irinotecan-induced neutropenia. The aim of this subset analysis is to investigate the association between these polymorphisms and toxicities in patients (pts) treated with FOLFIRINOX in the JASPAC 06 study.

Methods: JASPAC 06 study was a nationwide multicenter observational study of FOLFIRINOX for unresectable and recurrent pancreatic cancer. Pts who were screened for UGT1A1*6 and UGT1A1*28, and treated with either original FOLFIRINOX regimen (Oxaliplatin 85 mg/m^2, Irinotecan 180 mg/m^2, Levofolinate calcium [*l*-LV] 200 mg/m^2, bolus 5-FU 400 mg/m^2, and continuous 5-FU 2,400 mg/m^2, every two weeks) or modified regimen (Oxaliplatin 85 mg/m^2, Irinotecan 150 mg/m^2, *l*-LV 200 mg/m^2, and continuous 5-FU 2,400 mg/m^2, every two weeks) as first-line chemotherapy, were analyzed in this analysis.

Results: Of 399 eligible pts enrolled in JASPAC 06 study, 203 pts were eligible in this analysis. UGT1A1 was reported as wild (W) type (-/-) in 118 pts and heterozygous (H) type (-/*6, -/*28) in 81 pts. Remaining four pts with homozygote (*6/*6, *28/*28) or compound heterozygote (*6/*28) were excluded because of small population. Among 199 pts, 79 pts were treated with original regimen and 120 pts with modified regimen. In the original FOLFIRINOX group, 54/25 pts were W/H type. The median age was 60.5/60 years and PS0 was 57/52%. Incidences of grade 3/4 leukopenia, neutropenia, febrile neutropenia, diarrhea, anorexia and grade 4 neutropenia in pts with W/H type were 28/44%, 59/68%, 24/40%, 4/20%, 9/24% and 24/40%, respectively. In the modified FOLFIRINOX group, 64/56 pts were W/H type. The median age was 62.5/62 years and PS0 was 70/70%. The same toxicities as above were 22/27%, 44/50%, 5/7%, 16/7%, 14/9% and 16/20%, respectively.

Conclusions: Treated with original FOLFIRINOX regimen, pts with UGT1A1 heterozygous type experienced severe toxicities more frequently than those with wild type. In such cases, careful management of not only hematologic but gastrointestinal toxicities seems to be needed.

Legal entity responsible for the study: Shizuoka Industrial Foundation Pharma Valley Center

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741P Prognostic value of baseline neutrophil-to-lymphocyte ratio for predicting clinical outcome in metastatic pancreatic ductal adenocarcinoma (mPDAC) patients treated with liposomal irinotecan (nal-IRI) + 5-fluorouracil and leucovorin (5-FU/LV) vs 5-FU/LV alone

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Background: Elevated baseline neutrophil-to-lymphocyte ratio (NLR), a marker of subclinical inflammation, is associated with poor survival in several malignancies including mPDAC. Here we report the association of NLR with overall survival (OS) and progression-free survival (PFS) in a post-hoc analysis of the NAPOLI-1 trial (NCT01494506), that demonstrated improved survival with nal-IRI+5-FU/LV vs 5-FU/LV for treatment of mPDAC patients (pts) after disease progression following gemcitabine-based therapy.

Methods: Pts treated with nal-IRI+5-FU/LV or 5-FU/LV and available baseline NLR data were included (data cutoff: Nov 16, 2015). OS and PFS were assessed in pts with high (>5) or low (≤5) baseline NLR in individual and pooled treatment arms.

Results: Baseline NLR was available for 221 pts: 116/117 nal-IRI+ 5-FU/LV pts and 105/105 5-FU/LV pts. In the pooled treatment arms, pts with NLR≤5 had significantly better OS compared to pts with NLR >5 (6.2 vs 3.7 months, HR = 0.7, p = 0.02). Interestingly, this improvement in OS in pts with low vs high NLR was significant in the nal-IRI+5-FU/LV arm (8.4 vs 4.3 months, HR = 0.5, p=0.001); but not in the 5-FU/LV arm (4.8 vs 3.1 months, HR = 0.9, p=0.6). Similarly, PFS was significantly higher in pts with NLR≤5 vs NLR >5 in the pooled treatment arms (2.7 vs 1.4 months, HR = 0.7, p=0.05), and the nal-IRI+5-FU/LV arm (4.2 vs 1.4 months, HR = 0.5, p=0.002), but not the 5-FU/LV arm (1.5 vs 1.4 months, HR = 1.1, p=0.6).

Conclusions: Data from these exploratory analyses are consistent with previous reports on the prognostic value of baseline NLR in mPDAC, and extend it to the post-gemcitabine setting. Median OS and PFS were improved in pts with low vs high baseline NLR in the nal-IRI+5-FU/LV arm but not in the 5-FU/LV arm. Clinical implications of these data remain to be determined.

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Legal entity responsible for the study: Merrimack Pharmaceuticals, Inc.

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743P Tumor hyaluronan (HA) is a novel biomarker: Results of the randomized phase 2 HALO 202 study of PEGPH20 plus nab-paclitaxel/gemcitabine (PAG) vs AG in previously untreated, metastatic pancreatic ductal adenocarcinoma (mPDA)

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Background: PEGPH20 (P) degrades HA in the tumor microenvironment to increase access and therapeutic index of anticancer agents. In Stage 1 of this study, Halozyme Therapeutics, Inc. and Ventana Medical Systems, Inc., co-developed a novel HA assay, scoring algorithm, and cut-point, and showed improved progression-free survival (PFS) and objective response rate (ORR) in HA-High patients (pts) with PAG vs AG.

Table: 741P

	Pooled treatment arms		nal-IRI + 5FU/LV		5FU/LV	
Baseline NLR	≤5 (n = 155)	>5 (n = 66)	≤5 (n = 82)	>5 (n = 34)	≤5 (n = 73)	>5 (n = 32)
Median[1] OS, months (95% CI)	6.2 (5.2 - 7.6)	3.7 (3.1 - 4.4)	8.4 (6.1 - 10.2)	4.3 (3.4 - 4.7)	4.8 (3.6 - 6.1)	3.1 (1.9 - 4.2)
HR[2]	0.7		0.5		0.9	
95% CI	0.5 - 0.9		0.3 - 0.8		0.6 - 1.4	
P[3]	0.02		0.001		0.6	
Median[1] PFS, months (95% CI)	2.7 (2.4 - 3.3)	1.4 (1.4 - 1.6)	4.2 (3.1 - 5.6)	1.4 (1.4 - 2.8)	1.5 (1.4 - 2.6)	1.4 (1.3 - 1.9)
HR[2]	0.7		0.5		1.1	
95% CI	0.5 - 1.0		0.3 - 0.8		0.8 - 1.8	
P[3]	0.05		0.002		0.6	

[1]Medians reflect Kaplan-Meier estimates

[2]Hazard ratios (HRs) reflect Cox regression analysis.

[3]Two-sided p-value < 0.05 considered statistically significant in these exploratory analyses

Due to an imbalance in thromboembolic (TE) events in the PAG arm, the protocol was amended to add enoxaparin and exclude pts at high risk for TE events in Stage 2, which prospectively validated the algorithm and cut-point for the VENTANA HA RxDx assay.

Methods: In Stage 2, pts with mPDA were randomized 2:1 to PAG (P 3 μg/kg IV 2x/wk x 3 wk [C1], then 1x/wk x 3 wk [C2+] + AG) vs AG every 28 days. Endpoints were: primary—PFS and TE events; secondary—PFS by HA level, ORR; OS by HA level was exploratory. Tumor HA was evaluated using the VENTANA HA RxDx assay and algorithm; HA-High was defined by HA staining in the extracellular matrix ≥50% of the entire tumor surface at any intensity.

Results: 133 pts were enrolled; 125 pts were treated. As of December 16, 2016, an improvement in median PFS (91%) and median OS (50%) was observed in HA-High pts treated with PAG vs AG (Table), supporting tumor HA as a predictive marker for PEGPH20 efficacy. Among AG-treated pts, those with HA-High tumors showed poorer median PFS and median OS outcomes, suggesting that targeting tumor HA with PEGPH20 may improve the standard of care in mPDA.

Table: 743P

	PAG	AG	HR (95% CI)
HA-High	n = 24	n = 11	
PFS, months	8.6	4.5	0.63 (0.21-1.93)
OS, months	11.7	7.8	0.52 (0.22-1.23)
HA-Low	n = 53	n = 23	
PFS, months	6.0	7.2	1.21 (0.63-2.30)
OS, months	11.9	10.2	0.69 (0.38-1.23)

Conclusions: This is the first randomized Phase 2 study evaluating and supporting tumor HA as a potential predictive biomarker informing patient selection for PEGPH20 treatment, based on improvement in both PFS and OS in HA-High pts. The results provide support for the ongoing phase 3 HALO 109-301 study with co-primary endpoints of PFS and OS. NCT01839487.

Clinical trial identification: NCT01839487

Legal entity responsible for the study: Halozyme Therapeutics, Inc.

Funding: Halozyme Therapeutics, Inc.

Disclosure: A. Hendifar: Consulting or advisory role: Genentech, Novartis, Ipsen, Perthera. Travel, accommodations, expenses: Halozyme. A. Bullock: Consulting or advisory board participation support: Halozyme, Celgene, EMD Serono. T. Seery: Consulting or advisory role: Bayer. Speakers' Bureau: Ipsen, Bayer. L. Zheng: Consultancy or advisory role: Merrimack. Patents, royalties, other intellectual property: GVAX. Licensed to Aduro Biotech. Stock and other ownership: Z&L Medical Intl. Research funding: Bristol-Myers Squibb, Amgen, Iteos Therap, Gradalis, Merck, Halozyme. D. Sigal: Stock or other ownership: Novartis, BMS, Ignyta, Halozyme. Honoraria: Novartis, Serond, Halozyme. Speakers' Bureau: Novartis, Celgene, Bayer. Research funding: Halozyme. F.S. Braiteh: Author has disclosures to report for: Honoraria, Consulting or Advisory Role,Speaker's Bureau,Travels, Accommodation, Expenses. M. Zalupski: Research funding: Halozyme, OncoMed, Newlink Genetics. N. Bahary: Consulting or advisory role: Bayer/Onyx, EMD Serono. Research funding: New Links Genetics. W. Harris: Consulting or advisory role: Neotherma Oncology, Bayer. Research funding: Halozyme, BMS, Exelixis, Argule, Polaris, Medimmune, BTG. J. Pu: Employment: Roche; Research funding: Roche. Patents, royalties, other intellectual property: Roche (for author and institution). F. Lian: Stock or other ownership: Merck (Immediate Family Member). J. Zhu: Employment: Roche. Stock or other ownership: Roche. Honoraria: Roche. Travel, accommodations, expenses: Roche. W. Wu: Employment: Halozyme. Stock or other ownership: Halozyme. D. Chondros: Employee of Halozyme Therapeutics. P. Jiang: Employment: Halozyme. Stock or other ownership: Halozyme Therapeutics Inc. Patents, royalties, other intellectual property: Halozyme Therapeutics Inc. S.R. Hingorani: Consulting or advisory role: Halozyme, Aduro Biotech. Research funding to institution: Halozyme. All other authors have declared no conflicts of interest.

744P Overall survival and immunologic responses in metastatic pancreatic adenocarcinoma (PDAC) on PEGylated human IL-10 (AM0010) with 5-FU/LV and oxaliplatin (FOLFOX)

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Background: Median overall survival on 2nd line therapy of PDAC with 5-FU/LV plus oxaliplatin or nal-irinotecan is ~ 5-6 m. PDAC is refractory to immune therapies and mutational burden is relatively low and tumor infiltrating CD8+ T cells are rare. AM0010 stimulates survival, expansion and cytotoxicity of intratumoral CD8+ T cells and induced immune activation, durable stable disease and a 1yr survival of 22.5% in salvage PDAC pts. AM0010 has synergistic immune and anti-tumor activity with platinums and 5-FU in preclinical cancer models.

Methods: This phase 1b clinical study studied the safety and efficacy of AM0010 +FOLFOX as ≥ 2nd line treatment of PDAC. Pts who progressed on a median of 2 prior therapies (range 1-3) were treated with AM0010 (5ug/kg SQ, qd) + FOLFOX (n = 21). The safety population (n = 25) included four additional pts with prior FOLFOX. Tumor responses were assessed using irRC. Serum cytokines, activation of blood derived T cells and peripheral T cell clonality were analyzed. Pre-existing tumor infiltrating CD8 T cells were quantified by IHC.

Results: AM0010 + FOLFOX was generally well tolerated. G3/4 TrAEs included thrombocytopenia (52%), anemia (40%) and neutropenia (36%). Most cytopenias were transient and met retreatment criteria within 2-5 days. A modified AM0010 dose schedule of 5 days on, 2 days off avoided G3/4 cytopenias while retaining the immune stimulation. As of 05/1/2017, 2 pts have remained on treatment for > 72 weeks. 19 pts had tumor assessment following irRC (2 CR, 1 PR, 11 SD). The ORR and DCR were 15.8% and 74%. With a median follow-up of 14.2 m (range 6.8-18.9), 10 patients were alive (48%), mPFS and mOS were 3.5 and 10.2 m. Treatment induced a sustained cytokine increase in the serum and an expansion of novel T cell clones in the blood. This and a higher number of intra-tumoral CD8 T cells correlated with increased OS.

Conclusions: The combination of AM0010 with FOLFOX is well tolerated in patients with metastatic PDAC. This regimen induced sustained immune activation including the expansion of oligoclonal T cells. The prolonged tumor responses and OS are encouraging in this advanced population. This regimen is being studied in a phase 3 trial.

Clinical trial identification: NCT02009449

Legal entity responsible for the study: Armo BioSciences

Funding: ARMO BioSciences

Disclosure: A. Hung, G. Brown: Employee of ARMO BioSciences. P. Van Vlasselaer: Stock, leadership, employee of ARMO BioSciences. M. Oft: Employee of ARMO BioSciences. All other authors have declared no conflicts of interest.

745P Circulating levels of ADAM12, a stromal activation biomarker, are predictive of survival in pancreatic ductal adenocarcinoma (PDAC)

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Background: The dense stroma of PDAC promotes tumor growth and impedes delivery of cytotoxic drugs. We assessed the utility of ADAM12, a circulating biomarker of PDAC stroma identified in our preclinical models, to non-invasively measure stromal activation in patients (pts) and predict outcomes.

Methods: The prognostic and predictive value of ADAM12 was determined in an institutional cohort from the Academic Medical Center (AMC), which included 144 pts with PDAC (58 resected and 86 non-resected pts) and 38 non-age–matched healthy controls, and in a cohort of 372 pts with metastatic PDAC treated with *nab*-paclitaxel plus gemcitabine (*nab*-P/Gem) or Gem alone in the MPACT trial.

Table: 745P

	Overall Population		*nab*-P/Gem Arm		Gem Arm	
	Deaths, n/N (%)	Median OS (95% CI), mo	Deaths, n/N (%)	Median OS (95% CI), mo	Deaths, n/N (%)	Median OS (95% CI), mo
FC < 1	98/112 (88)	9.7 (8.7 - 11.6)	52/59 (88)	11.2 (9.6 - 14.0)	46/53 (87)	8.7 (6.9 - 9.5)
FC > 1	54/58 (93)	8.1 (6.5 - 9.9)	25/27 (93)	8.3 (6.5 - 11.3)	29/31 (94)	6.9 (5.5 - 9.3)
ND	30/38 (79)	13.2 (9.3 - 16.4)	17/22 (77)	14.4 (8.5 - 19.2)	13/16 (81)	12.0 (6.8 - 14.9)
HR (95% CI); *P* value						
FC < 1 vs ND FC > 1 vs ND FC < 1 vs FC > 1	1.5 (1.0 - 2.3); < .05 2.3 (1.4 - 3.6); < .01 0.7 (0.5 - 0.9); .02		1.8 (1.0 - 3.2); .04 2.8 (1.5 - 5.4); < .01 0.6 (0.4 - 1.0); .07		1.3 (0.7 - 2.3); .48 1.7 (0.9 - 3.3); .11 0.7 (0.5 - 1.2); .19	

BL, baseline; FC, fold change; HR, hazard ratio; *nab*-P/Gem, *nab*-paclitaxel plus gemcitabine; ND, no detectable; OS, overall survival; pt, patient.

Results: For the AMC cohort, higher serum ADAM12 levels (median, 372 pg/mL; $P < .01$) were found in pts with PDAC vs healthy controls (median, 154 pg/mL). High ADAM12 levels (> median) were significantly associated with poor survival ($P = .04$) in resected pts but not in non-resected pts ($P = .67$). In the pooled MPACT analysis, median overall survival (OS) was significantly longer (9.3 vs 6.9 months; log-rank $P = .01$) in pts with no detectable (ND; n = 95) vs detectable (n = 277) serum ADAM12 levels at baseline (BL). Median OS was longer in pts with ADAM12 decrease (fold change [FC] < 1) vs increase (FC > 1) from BL to cycle 2, but both OS values were significantly shorter than that in pts with ND ADAM12 levels at either time point (Table).
In a multivariate analysis, baseline ADAM12 levels (0 vs > 0; $P = .02$), treatment (*nab*-P/Gem vs Gem; $P = .02$), and Karnofsky performance status (90-100 vs 70-80; $P < .01$) were significant predictors of OS. Table. OS in pts with ADAM12 measured at both BL and cycle 2 in the MPACT study

Conclusions: Low serum levels of ADAM12 at baseline were associated with longer OS in pts with PDAC, as were decreases in ADAM12 during treatment. ADAM12 may be a valuable biomarker to predict long-term outcomes in pts treated with *nab*-P/Gem.

Legal entity responsible for the study: Celgene Corporation

Funding: Celgene Corporation

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746P COnsensus statement on mandatory measurements in PAncreatic cancer trials for systemic treatment of unresectable disease (COMM-PACT)

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Background: Variations in the reporting of potentially confounding variables in studies investigating systemic treatments of unresectable pancreatic cancer challenge adequate comparisons. We establish the first international consensus on mandatory baseline- and prognostic characteristics to be taken into account in future pancreatic cancer trials for patients with unresectable disease.

Methods: A systematic review was performed for phase III trials investigating first-line systemic therapy for unresectable pancreatic cancer that were published between January 2000 and January 2016 to identify baseline characteristics and prognostic variables. The electronic databases Medline, EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL) were used. A structured overview was created demonstrating the reporting frequencies of baseline characteristics and prognostic relevance of identified variables. A modified Delphi panel of two rounds involving 23 leading medical-oncologists in the field of pancreatic cancer was used to develop the consensus.

Results: A total of 624 studies were identified. After screening, 39 randomized controlled trials (RCTs) with 15,863 patients were included. Thirty-two baseline characteristics and 26 prognostic characteristics were identified. After two consensus rounds, 24 baseline characteristics and twelve prognostic characteristics were designated as a mandatory reporting set for future trials. Table 1. Mandatory set

Table: 746P

Baseline characteristics	Prognostic characteristics
Age	Age
Albumin	Albumin
Biliary stent	Bilirubin
Bilirubin	CA 19.9
CA19.9	CRP
C-Reactive Protein (CRP)	Disease status
Disease status	LDH
Gender	Liver metastasis
Histology	NLR
LDH	Number of metastatic sites
Liver metastasis	Pain at baseline
Loss of weight > 10%	Performance status
Neutrophil lymphocyte ratio (NLR)	
Number of metastatic sites	
Pain at baseline	
Performance status	
Peritoneal metastasis	
Primary tumor location	
Prior chemotherapy/radiotherapy	
Prior surgery	
Pulmonary metastasis	
Time from diagnosis	
Tumor differentiation	
Weight/BMI	

Conclusions: The COnsensus statement on Mandatory Measurements identifies a set of baseline- and prognostic characteristics in unresectable PAncreatic Cancer Trials (COMM-PACT) that allows for adequate comparison of outcomes between studies.

Legal entity responsible for the study: Not applicable

Funding: None

Disclosure: All authors have declared no conflicts of interest.

747P Phase I study of resminostat/S-1 combination in patients with pre-treated biliary tract or pancreatic cancer

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Background: Resminostat is an oral hydroxamate-type inhibitor of class I, IIb, and IV histone deacetylases. S-1 is preferably used in biliary tract (BTC) and pancreatic cancer (PC) in Japan. However, patients (pts) with high thymidylate synthase (TS) expression are known to show resistance to S-1. Resminostat down-regulates TS expression and has shown additive effects to S-1 in preclinical studies. Thus, resminostat besides its antitumor activity, may overcome S-1 resistance by down-regulating TS. We report a Japanese phase I study of resminostat + S-1 combination therapy in a 2nd-line or later setting for BTC/PC.

Methods: In the first stage, we determined the optimal dosing schedule for resminostat + S-1 combination therapy, investigating its safety and efficacy in the second stage. In the former, pts were treated with one of the following 3 regimens (R): R1, resminostat 200 mg/day on Day 1 to 14 every 21 days; R2, resminostat 200 mg/day + S-1 80 to 120 mg/day according to BSA on Day 1 to 14 every 21 days; or R3, resminostat 200 mg/day on Day 1 to 5 and Day 8 to 12 ("5 + 2" dosing schedule) + S-1 80 to 120 mg/day according to BSA on Day 1 to 14 every 21 days. In the latter, additional 10 pts were treated with the regimen selected in the first stage. Dose-limiting toxicities (DLTs) were evaluated according to adverse drug reactions observed during the first cycle in the first stage.

Results: A total of 27 pts were enrolled (first stage: R1, 6 pts; R2, 5 pts; R3, 6 pts; second stage: 10 pts). Two DLTs were observed: one (Grade 2 anorexia) in a patient treated with R2 and one (Grade 3 stomatitis) in another patient treated with R3. Dose modification due to gastrointestinal toxicities was implemented frequently in pts treated with R2. Therefore, R3 was selected as the regimen for the second stage. A total of 16 pts (BTC 13 pts; PC 3 pts) were treated with R3 and it was well tolerable. Disease control rate was 81.3% (BTC 84.6%; PC 66.7%). The median progression-free survival was 3.1 months (BTC 5.5 months; PC 2.3 months).

Conclusions: The data revealed that R3 ("5 + 2" dosing schedule of resminostat in combination with S-1) was well tolerated in advanced BTC/PC pts. Further investigations are warranted for its efficacy especially in advanced BTC pts.

Clinical trial identification: JAPIC Clinical Trials Information (JapicCTI-152864)

Legal entity responsible for the study: Yakult Honsha Co., Ltd.

Funding: Yakult Honsha Co., Ltd.

Disclosure: C. Morizane: Consulting or Advisory Role: AstraZeneca, Yakult, Novartis, Taiho Honoraria: Pfizer, Novartis, Yakult Honsha, Lilly, Nobelpharma, Fujifilm Research Funding: GlaxoSmithKline, Pfizer, Nobelpharma, Eisai, Yakult, Ono Pharmaceutical, Taiho. I. Ohno: Consulting or Advisory Role: Merck Serono. H. Ueno: Honoraria: Taiho, Chugai, Yakult Research Funding: Taiho, Eli Lilly, NanoCarrier, Baxalta, Yakult. S. Mitsunaga: Honoraria: Ono pharmaceutical, Toray Research Funding: Bayer Yakuhin, Chugai Pharmaceutical, Merck Serono, Aslan Pharmaceuticals, Ajinomoto. Y. Hashimoto: Honoraria: Taiho pharmaceuticals, Boston scientific, Olympus Medical Research funding: Taiho pharmaceuticals Travel, Accomodations, Expenses: Taiho pharmaceuticals, M.I.Tech. T. Okusaka: Research funding from Yakult Honsha Co., Ltd. S. Kondo: Research funding: Astrazeneca, Eli Lilly, Pfizer, Bayer, MSD, ASLAN. H. Takahashi: Honoraria: Taiho Pharmaceutical Research funding: Bayer Pharmaceutical, Bristol-Myers Squibb Travel, Accomodations, Expenses: Pfizer Inc. R. Hara: Employee and stock owner at Yakult. S. Kobayashi, O. Nakamura: Employee of Yakult. M. Ikeda: Honoraria: Novartis, Taiho, Chugai, Daiichi Sankyo, Lilly, Yakult Membership on an advisory board: Nano Carrier Corporate-sponsored research: Yakult, Taiho, Ono, Eisai, AstraZeneca, Zeria, Merck Serono, Baxter, Nano Carrier. All other authors have declared no conflicts of interest.

748P Comparisons of outcomes of patients with advanced pancreatic cancer (APC) treated with FOLFIRINOX (FX) versus gemcitabine and nab-paclitaxel (GN): A population-based cohort study

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Background: FX and GN are more active than gemcitabine in patients with APC. However, it is not known if FX is superior to GN in APC. In the absence of a randomized controlled trial this population-based cohort study is undertaken to compare efficacy and safety of the two standard regimens in APC.

Methods: All patients with newly diagnosed locally APC in the province of Saskatchewan, Canada, during 2011-2016 who received FX or GN, were assessed. A Cox proportional multivariate analysis was done to evaluate correlation of chemotherapy regimen and survival.

Results: 119 eligible patients with median age of 61 yrs (IQR:56-67) & M:F of 70:49 were identified. 93% had WHO performance status (PS) of 0 or 1, and 77% had metastatic PC. 15% received adjuvant therapy and 33% had ≥2 metastatic sites. Of 119 patients, 86 (72%) received FX and 33 (28%) treated with GN. There were significant differences between the two groups with respect to age (59 vs. 64 yrs), WHO PS of 2 (2% vs. 15%) and metastatic disease (81% vs. 64%), in FX and GN groups, respectively. Median progression-free survival of FX group was 6 months (95%CI: 4.5-7.5) vs. 4 months (2.9-5.1) with GN ($p = 0.39$). Median overall survival (OS) with FX was 9 months (7-11) vs. 9 months (4.2-13.8) with GN ($p = 0.88$). At 12 months 26% & 27% patients were alive in FX and GN groups, respectively. Median OS of patients who received 2nd line therapy was 15 months (10.5-19.5) vs. 8 months (6.3-9.7) with no 2nd line therapy (0.009). Patients in FX had higher incidences of any grade diarrhea (52% vs.18%), mucositis (21 vs. 3), neuropathy (63 vs.36) and thromboembolism (34 vs. 9) whereas patients in GN group had more often fatigue (66 vs.79) and thrombocytopenia (48 vs. 57). On multivariate analysis normal albumin, HR:0.63 (0.41-0.97), male sex, HR:0.65 (0.43-0.97) and 2nd line therapy, HR:0.50 (0.28-0.86) were correlated with better survival but no correlation between FX or GN and survival was noted.

Conclusions: Our results showed that real world patients with APC treated with FX or GN had comparable survival with different safety profiles. In this selected patients who received combination therapy, male gender and subsequent treatment were correlated with better survival.

Legal entity responsible for the study: N/A

Funding: None

Disclosure: All authors have declared no conflicts of interest.

749P Musculoskeletal Events (MSEs) with PEGPH20 treatment and management in patients with previously untreated metastatic pancreatic ductal adenocarcinoma (mPDA)

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Background: Hyaluronan (HA) accumulation in the tumor microenvironment is associated with poor outcomes. PEGylated recombinant human hyaluronidase PH20 (PEGPH20) degrades HA, facilitating access of cancer therapies. MSEs (e.g., muscle spasms, arthralgia, and myalgia) occur frequently with PEGPH20, and were dose-limiting in Phase 1 studies. Here we describe MSEs observed in a phase 2 study of PEGPH20 (P) plus gemcitabine/nab-paclitaxel (AG) vs AG in patients with previously untreated mPDA.

Methods: In Stage 1 of the study, patients were randomized 1:1 to PAG or AG (P 3 μg/kg IV 2x/wk x 3 wks in Cycle 1, then once weekly x 3 wks in Cycle 2+) every 28 days. A clinical hold due to an imbalance in thromboembolic events resulted in ~40% of patients discontinuing PEGPH20. After the clinical hold, patients were randomized 2:1 to PAG vs AG (Stage 2). Dexamethasone 8 mg was administered orally within 2 hours before and 8-12 hours after PEGPH20 to lessen the severity of MSEs. We analyzed adverse event frequency, severity, timing, and management.

Results: 279 patients were enrolled; 260 patients comprise the safety population. All patients received a median of 3.3 months of study treatment. The proportion of patients with treatment-emergent MSEs was higher in the PAG arm vs AG arm (all grade, 86% vs 46%; grade 3, 19% vs 6%). Grade 4/5 MSEs were not observed. The most common MSEs (all grade/grade 3, PAG vs AG) were muscle spasms in lower and upper extremities (58%/13% vs. 6%/1%), arthralgia (28%/2% vs.14%/1%) and myalgia (27%/5% vs.12%/0). Median (range) time to MSE onset was 2 (0-287) days for PAG and 8 (0-196) days for AG. Median duration of Grade 3 MSEs was 9 (5-14) days for PAG vs 8.5 (2-22) days for AG. Five (4%) patients experienced MSEs that led to PAG discontinuation: muscle spasms ($n = 4$) and myalgia ($n = 1$). Medications were administered in 57% (PAG) vs. 20% (AG) of MSE episodes, predominantly to manage Grade 3 MSEs.

Conclusions: MSEs are commonly observed with AG treatment, and even more frequently with PAG. MSEs are primarily mild (Grade 1/2) and infrequently lead to treatment discontinuation. The time course, associated dose modifications, and management of MSEs will be presented.

Clinical trial identification: NCT01839487

Legal entity responsible for the study: Halozyme Therapeutics, Inc.

Funding: Halozyme Therapeutics, Inc.

Disclosure: A. Bullock: Consulting or advisory board participation support: Halozyme, Celgene, and EMD Serono. P. Vervaet, W. Wu, D. Chondros: Employee of Halozyme Therapeutics. S.R. Hingorani: Consulting or Advisory Role: Halozyme, Aduro Biotech Research Funding: Halozyme (institution). A. Hendifar: Consulting or Advisory Role: Genentech, Novartis, Ipsen, Perthera Travel, Accommodations, Expenses: Halozyme.

750P Phase Ib study of PF-04136309 (an oral CCR2 inhibitor) in combination with nab-paclitaxel/gemcitabine in first-line treatment of metastatic pancreatic adenocarcinoma

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Background: CCL2/CCR2 plays a key role in immunosuppressive properties of the pancreatic adenocarcinoma tumor microenvironment (TME), patients' (pts) prognosis and chemoresistance. PF-04136309 (oral CCR2 inhibitor) blocks recruitment and migration of inflammatory monocytes (IM) from bone marrow (BM) to TME.

Methods: This ongoing multicentre phase Ib study is investigating PF-04136309 in combination with nab-paclitaxel and gemcitabine (nab-P+Gem) in pts with previously untreated metastatic pancreatic ductal adenocarcinoma (mPDAC). Objectives; primary: safety, tolerability, maximum tolerated dose, recommended dose; secondary: pharmacokinetics (PK), pharmacodynamics of PF-04136309; exploratory: efficacy, proof of mechanism (POM), as CCR2 inhibition trapped IMs in BM and decreased IMs in peripheral blood and metastatic tumor tissue with paired tumor biopsies and bone marrow aspirates at baseline and after 1 or 2 cycles.

Results: From May 1, 2016–March 17, 2017, 21 pts (ECOG PS 0-1; mean age 61.8 yrs; range 46-79) received PF-04136309. Cohort 1, starting dose level: 1 grade 3 drug-related DLT (cognitive disorder), 1 grade 2 and 2 grade 1 rashes. Cohort 2 (1 dose level reduction): 4 (23.5%) grade 3 drug-related DLT (1 scalp dysesthesia, 1 ALT-AST, 1 pneumonia, 1 pneumonitis). Recommended total daily dose 1000mg. With median duration of treatment of 4 mo (1–9), grade $\geq$3 drug-related AEs: neutropenia 3 (17.6%), fatigue 4 (23.5%), diarrhea 1 (5.9%), lung toxicities 3 (17.6%); % pts with dose-reduction: nab-P 47%, Gem 53%, PF-04136309 41%; median relative dose intensity: nab-P 84%, Gem 67%, PF-04136309 80%. Early objective response in 10 evaluable pts: PR 6 (60%), SD 1 (10%), PD 3 (30%). Disease control rate at 4 mo: 70%. Median PFS not reached (8 pts on treatment). PF-04136309 PK was consistent with previous single agent studies. Almost all had a drop in peripheral blood CD14+CCR2+ monocytes (baseline-Day 15). IMs decreased and CD4+ and CD8+ T cells increased (5–8 fold) in paired biopsy samples. One of 2 pts had increased tumor associated PD1+CD4+ and PD-1+CD8+ T cells.

Conclusions: Encouraging safety, favorable PK, clinical responses and POM with CCR2 inhibition plus nab-P+Gem in mPDAC pts.

Clinical trial identification: NCT02732938.

Legal entity responsible for the study: Pfizer Inc.

Funding: Pfizer Inc.

Disclosure: M. Noel: Speaker's bureau for Taiho Oncology. M. Lowery: Advisory board: Agios Pharmaceuticals, Celgene. D. Ryan: MPM Capital. C. Britten: Research paid to institution: Pfizer. B. Jin, C.T. Taylor, B.J. Ganguly, D. Yin, E.C. Gamelin, D.A. Wunderlich: Employee and stockholder of Pfizer Inc. All other authors have declared no conflicts of interest.

751P Metastatic pancreatic cancer: Real Life data from the german quality of life and translational research on pancreatic cancer study (QoliXane)

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Background: Recently, nab-paclitaxel/gemcitabine (NPG) became new standard first-line therapy for metastatic pancreatic cancer. Based on this, our study group has established QoliXane for metastatic pancreatic cancer patients receiving 1st line NPG, to deliver real life and Quality of life (QoL) data and build a platform for translational research (TR). This is an interim analysis of our data focused on efficacy outcome.

Methods: In this a non-interventional registry study, eligible patients were recruited after written informed consent from 95 German cancer centers. The course of therapy, efficacy-, QoL- data (prior to and during therapy) and archival tumor material were prospectively collected. In the present analysis, efficacy endpoints were analyzed in the intention-to-treat population (ITT), defined as all patients who were enrolled.

Results: 539 patients fulfilled the criteria of the ITT. Median age was 70 y (39-86). At the time of analysis, 301 (56%) pts of the ITT were alive. Mean no. of metastatic sites involved was 2. Median no. of cycles administered was 3 (range 0-6). 231 (43%) pts needed any dose modification and 209 (39%) received further therapies beyond progression. 70 (13%) pts had increased bilirubin at baseline, 18 (26%) of them had an intervention e.g. ERCP. Subjects with increased bilirubin without intervention received a median of 3 cycles, with decreasing values under therapy. 135 (25%) pts developed polyneuropathy of any grade. Median progression-free survival was 6 months (95% CI; [5- 6]). Median overall survival (OS) was 10 months (95% CI [8- 10]). 1-year OS was 40%. Median survivals by ECOG PS of 0, 1, 2, and 3 were 12 months, 9 months, 5 months, and 2 months, respectively ($p<.001$).

Conclusions: The "QoliXane" shows excellent real life efficacy data for 1st line therapy with NPG in Germany. In the expansion phase, QoliXane will transform into a permanent, high quality, prospective registry, covering all therapy lines. QoL and translational research data will follow.

Clinical trial identification: NCT02691052

Legal entity responsible for the study: Al- Batran

Funding: Celgene

Disclosure: All authors have declared no conflicts of interest.

752P FOLFIRINOX as second-line chemotherapy for advanced pancreatic cancer: A subset analysis from the nation-wide multicenter observational study (JASPAC06)

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Background: The data of FOLFIRINOX as second-line chemotherapy in advanced pancreatic cancer are very limited. The JASPAC06 study, a nation-wide multicenter observational study of FOLFIRINOX for the patients with unresectable or recurrent pancreatic cancer as any line treatment, showed the favorable efficacy and safety in Japanese clinical practice.

Methods: The subjects were the patients with unresectable/recurrent pancreatic cancer who received FOLFIRINOX as second-line chemotherapy.

Results: Of the 399 evaluable patients in the JASPAC06 study, 44 patients were eligible. Patients characteristics were; median age, 62 years; male, 26(59%); ECOG-PS0/1, 30(68%)/14(32%); disease status recurrent/locally/metastatic, 4(9%)/8(18%)/32(73%); biliary drainage, 11(25%); UGT1A1 status *28 and *6 wild/single heterozygous/homozygous or double heterozygous/unknown, 25(57%)/16(36%)/2(5%)/1(2%). The initial dose was reduced in 28(64%) patients. The median time to treatment failure and the number of cycles were 4.5 (range, 6-573 days) months and 6 cycles (range, 1-13 or more). The major grade 3/4 adverse events were neutropenia in 29(66%) patients, leucopenia in 17(39%), anorexia in 7(16%), febrile neutropenia in 5(11%) and anemia in 5(11%). Fatal adverse event occurred in 1 patient, which was a sudden death. The median overall survival, progression free survival and 1-year survival rate were 10.1 (95%CI, 7.1-13.1), 4.1 (95%CI, 1.5-6.8) months and 41.0%, respectively. The overall response rate and disease control rate were 28% and 65%. The reasons for discontinuation of FOLFIRINOX, excluding 2 patients ongoing treatment, were tumor progression in 38(86%) and toxicity in 4(9%).

Conclusions: It was suggested that FOLFIRINOX as second-line chemotherapy in advanced pancreatic cancer was effective for the patients with good PS and toxicity was similar to that as the first-line treatment.

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Legal entity responsible for the study: N/A

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753P Quality of life (QoL) of patients (pts) with metastatic pancreatic cancer (mPAC) initiating first-line chemotherapy (CT) in routine practice

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Background: Considering the physical decline of mPAC pts, the assessment of QoL becomes a matter of major concern. We aimed to assess the QoL of mPAC pts treated with first-line CT in routine practice.

Methods: Observational, prospective, multicenter study including mPAC pts who started first-line CT between 2014 and 2015 in 12 Spanish centers. Treatment and clinical characteristics were recorded at CT start (baseline [BL]). The patients' QoL, ECOG, and Karnofsky index (KI) were measured at BL, at days 15 and 30, and every 4 weeks up to 6 mo of CT. QoL was measured using the EORTC QLQ-C30 global health status questionnaire (QLQ). Other variables included treatment response, overall survival (OS), and progression-free survival (PFS).

Results: The study sample included 117 pts with a median age of 65 years (range 37-84). Metastases were mostly hepatic (75%). At BL, median weight loss (last 3 mo) was 9.2%, ECOG was 0-1 and 2 in 82% and 18% of pts, respectively, and KI was 70-80 and 90-100 in 48% and 52% of pts, respectively. Main first-line CT was gemcitabine in monotherapy (19%) or combined with nab-paclitaxel (65%). Overall, median OS and PFS were 9.0 mo (95% CI 6.4-10.6) and 6.0 mo (4.6-7.8), respectively; 3% and 28% of pts achieved a complete and partial response, respectively, with stable disease in 39% of pts. During the follow-up, 64% of pts improved their QoL; the KI showed no significant changes. Of 19 pts with BL ECOG 2, between 67% and 100% had improved their QLQ score at visits at the 1st mo and following. At BL, pts with KI 70-80 had poorer QoL, but experienced a greater improvement than those with KI 90-100 ($p = 0.015$), reaching similar QLQ scores after 2 mo of CT. A similar trend was observed in pts with ECOG 0-1 vs. 2 ($p < 0.001$). Pts improved their QoL irrespective of their weight loss, but those with weight loss $\leq$10% had greater QLQ scores throughout the follow-up ($p = 0.028$). Median OS was higher in pts with BL QLQ $\geq$50 ($p = 0.015$), KI 90-100 ($p = 0.047$), and weight loss $\leq$10% ($p = 0.048$).

Conclusions: The EORTC QLQ-C30 questionnaire is suitable for measuring the QoL of mPAC pts undergoing CT. BL QLQ-C30 $\geq$50, KI 90-100, and weight loss $\leq$10% were associated with a greater OS. Most pts improved their QoL during CT, including those with poorer ECOG and KI at BL.

Clinical trial identification: CEL-CPM-2014-01

Legal entity responsible for the study: Celgene, S.L.

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Disclosure: M. Martín, A. García: Temporary consultant collaborator with Celgene. L. Pellín, D. Vilanova: Employee of Celgene. All other authors have declared no conflicts of interest.

754P Impact of the duration of diabetes mellitus (DM) on the outcomes of metastatic pancreatic cancer (mPC) treated with gemcitabine (G): A retrospective study

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Background: While previous studies showed that patients (pts) with PC and long-standing DM had worse survival than pts without DM, the impact of the duration of DM on therapeutic outcomes has not been sufficiently studied in pts receiving chemotherapy for mPC.

Methods: We retrospectively analyzed the therapeutic results for pts with mPC who received G as standard therapy before the introduction of combination regimens at two sites of the National Cancer Center ("Tokyo" and "Kashiwa"). The efficacies and toxicities of G were compared among three groups classified by the DM duration: no DM, short-term DM (< 4 years), and long-term DM (≥ 4 years). To examine the associations of the DM duration with overall survival (OS) and progression free survival (PFS), Cox proportional hazards model was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) adjusted for the baseline characteristics.

Results: Overall, 350 pts ("Tokyo": n = 202, 2008-2013; "Kashiwa": n = 148, 2008-2011), were included: 218, 87, and 45 in the no DM, short-term DM, and long-term DM groups, respectively. No statistically significant differences in baseline characteristics were observed among the three groups except for BMI (median [kg/m^2]: 20.7, 21.4, and 22.5; $p = 0.015$, Kruskal–Wallis test). Compared with the no DM group, multivariable-adjusted HRs for PFS were 1.33 (95% CI, 0.94-1.89; $p = 0.103$) for the long-term DM group and 1.12 (95% CI, 0.85-1.47; $p = 0.410$) for the short-term DM group; and those for OS were 1.37 (95% CI, 0.95-1.98; $p = 0.096$) and 1.10 (95% CI, 0.82-1.46; $p = 0.533$), respectively. There were no substantial differences in HRs between "Tokyo" and "Kashiwa" (e.g., HRs of long-term DM for PFS were 1.54 [95% CI, 0.98-2.44] and 1.33 [95% CI, 0.80-2.21], respectively; HRs of long-term DM for OS were 1.32 [95% CI, 0.82-2.14] and 1.34 [95% CI, 0.80-2.26], respectively). Also, HRs for PFS and OS did not substantially change with different cutoff years of DM duration (ranges of HRs of long-term DM with cutoff at 3-5 years: PFS, 1.36-1.55; OS, 1.21-1.33). No significant differences in tumor response and toxicity were observed.

Conclusions: A long pretreatment history of DM may be associated with a shorter PFS and OS among pts with mPC.

Legal entity responsible for the study: National Cancer Center Hospital

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755P Prognostic value of neutrophil-lymphocyte ratio in first line treatment for metastatic pancreatic adenocarcinoma

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Background: Tumor location and pro-inflammatory microenvironment are both implicated in cancer progression and thus measures of these are thought to have important prognostic value. In this study, these readily available factors were examined in patients diagnosed with metastatic pancreatic adenocarcinoma (mPC) being treated in first line with FOLFIRINOX (FFX) or Gemcitabine with nab-Paclitaxol (GNP).

Methods: A cohort of 75 patients diagnosed with mPC between 2010 – 2016 and treated either with FFX or GNP first line were analyzed. The NLR was calculated based on the complete blood count obtained on the day of the first treatment. Cox proportional hazard models were used to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) associating progression free survival to the patients' demographics, treatment, clinical and pathological factors. NLR was treated as a continuous covariate.

Results: Of the total patients (60% male, median age 69), 44 (58.7%) were treated with FFX. At the time of diagnosis, 20 (26.6%) presented with ECOG 0, 43 (57.3%) with primary disease at the head of the pancreas and 25 (33.3%) with liver metastasis. Median NLR at the diagnosis was 5.35 (range 0.9 – 28.3). Increasing NLR was a significant prognostic factor for shorter PFS using a univariate model (HR 1.08, CI: 1.009 – 1.15, P = 0.026). In a multivariate model, significant prognostic factors associated with shorter PFS included primary disease location at the pancreatic tail/body (HR 1.92, CI: 1.009 – 3.664, p = 0.047) and higher NLR (HR 1.11, CI: 1.038-1.189, P = 0.002).

Conclusions: Understanding the prognostic value of pro-inflammatory status and tumor location can allow clinicians to better manage the trajectory of patients with mPC.

Legal entity responsible for the study: Lady Davis Institute and Segal Cancer Centre - Jewish General Hospital

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756P Treatment patterns, clinical characteristics, and outcomes of patients (pts) with metastatic pancreatic cancer (MPC) treated with nab-paclitaxel (nab-P) plus gemcitabine (GEM) in real-life practice: ANICE-Pac trial

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Background: Combined treatment of nab-P plus GEM increases survival in patients with MPC. However, treatment efficacy and safety need to be assessed in real-life practice, including pts irrespective of their clinical characteristics and number of dose administrated and treatment duration.

Methods: Retrospective, multicenter study including pts with MPC who started first-line treatment with nab-P plus GEM between December 2013 and June 2015 according to routine clinical practice. Overall survival (OS) and progression-free survival (PFS) were assessed for the total sample and the exploratory subgroups based on treatment and clinical characteristics of pts.

Results: 210 pts (60% males) were enrolled with a median age of 65 years (range 37 – 81); 25% were $\geq$ 70 years. MPC was de novo and recurrent in 78% and 22% of pts, respectively; 18% had a biliary stent. At baseline, 53% of pts had Neutrophil lymphocyte rate (NLR)$>$ 3, 82% CA 19.9 $>$ 35 U/mL, and 18% ECOG $\geq$ 2. Pts received a median of 4 cycles (1 – 21); 32% started treatment with a dose reduction and 17% received $\leq$ 30 days of treatment, mainly due to toxicity (33%) or progression (30%); 25% of pts achieved objective response, and median OS and PFS were 7.2 (95%CI 6.0 – 8.5) and 5.0 (4.3 – 5.9) months (mo), respectively. Compared with pts treated during $>$ 30 days, those with $\leq$ 30 treatment had lower OS (8.6 [7.2 – 10.2] vs. 1.9 [0.8 – 2.3] mo; $p < 0.001$). OS was not influenced by age $\geq$ vs $<$ 70 years ($p = 0.205$) and the presence of a biliary stent ($p = 0.195$), but it was significantly lower in pts with baseline NLR $>$ 3 ($p = 0.002$), CA 19.9 $>$ 35 U/mL ($p = 0.002$), and ECOG $\geq$ 2 ($p = 0.018$); 29% pts experienced at least one grade 3-4 adverse event, mostly neutropenia (14%).

Conclusions: Our results revealed that real-life MPC pts tend to be older and have worse performance status (ECOG) than those included in clinical trials with restrictive selection criteria. In fact, many pts either did not complete 1 month of treatment or started treatment with a dose reduction. Despite these limitations, nab-P plus GEM remains effective in this clinical setting. ECOG $\geq$ 2, NLR $>$ 3, and CA 19.9 $>$ 35 U/mL are associated with lower OS.

Clinical trial identification: GIT-ADE-2015-02

Legal entity responsible for the study: Galician Group for the Treatment of Digestive Tumors (GITuD)

Funding: Galician Group for the Treatment of Digestive Tumors (GITuD)

Disclosure: A. García: Received honoraria from Celgene. C. Guillén: Consultant/advisor board member for Celgene, and received remuneration for traveling and accomodations by Celgene. All other authors have declared no conflicts of interest.

757P Safety and efficacy of gemcitabine/nabpaclitaxel in elderly patients with metastatic or locally advanced pancreatic adenocarcinoma: a retrospective analysis

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Background: Gemcitabine/nabpaclitaxel is a polychemotherapy regimen currently used to treat metastatic pancreatic cancer patients with a good performance status (PS). Gemcitabine/nabpaclitaxel significantly improves overall survival (OS) and progression free survival (PFS), but few data are available in elderly patients. Therefore, we carried out a retrospective analysis to evaluate efficacy and safety profile of this combination in a cohort of elderly patients.

Methods: All cases of metastatic pancreatic adenocarcinoma in patients over 70 years old treated at our Department between 2014 and 2016 with gemcitabine/nab-paclitaxel were retrospectively reviewed. The primary objective was to evaluate the safety and efficacy of this regimen in the elderly population.

Results: Forty-six patients with a median age of 73 years (range: 70-79) were included in this analysis: males: 19 (41%); PS2: 6 (13%); primary location: head 26 (57%); biliary stent:14 (30%); previous surgery: 5 (11%); adjuvant CT 5 (11%). Overall response rate (ORR) was 33.3%; median progression-free survival (PFS) was 7 mo (95% CI 5.89-9.10) and median overall survival (OS) was 12 mo (95% CI 10.7-16.13). Treatment was well tolerated. No grade 4 toxicity was reported. Grade 3 toxicity included neutropenia in 5 pts (10%), peripheral neuropathy in 2 pts (4.3%), thrombocytopenia in 2 pts (4%), diarrhea in 3 pts (6.5%), nausea and vomiting in 1 pt (2.1%), and fatigue in 2 pts (4.3%). No significant difference in terms of efficacy and safety was recorded with a cohort of 50 pts under 70 years of age: ORR: 36.6%; median PFS 6.7 mo (95% CI 5.966-8.034), and median OS 10.5 mo (95% CI 7.864-12.136). Finally, pain control was achieved in 15 of 24 patients (62.5%) with a performance status improvement of 10% according to the Karnofsky scale.

Conclusions: Although pancreatic cancer mostly affects elderly people, clinical trials often include few elderly pts. These data suggest that combination of gemcitabine plus nab-paclitaxel is effective and safe in an unselected population of elderly pts showing no differences in outcome between older patients and younger patients treated with this combination.

Legal entity responsible for the study: University of Campania Luigi Vanvitelli

Funding: None

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758P Updated results of a phase II study of gemcitabine, erlotinib, and S-1 in patients with advanced pancreatic cancer

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Background: Gemcitabine-based chemotherapy is considered as a standard front-line treatment for patients with advanced pancreatic cancer. Although addition of erlotinib or S-1 to gemcitabine has yielded better outcomes, it has showed just modest improvement in survival. To overcome this limitation, we evaluated the efficacy and safety of the combination of gemcitabine, erlotinib, and S-1 for the treatment of advanced pancreatic cancer.

Methods: Chemotherapy-naïve patients with pathologically proven locally advanced, recurrent or metastatic pancreatic adenocarcinoma were assessed for eligibility. Gemcitabine at 1,000 mg/m^2 was administered intravenously on day 1, and 8, erlotinib at 100 mg/day was administered on days 1-21, and S-1 at 60 mg/m^2 was administered on days 1-14 every 21 days and continued to maximum of 8 cycles of treatment. Dose escalation of S-1 to 80 mg/m^2 was permitted from second cycle for pre-defined tolerable patients.

Results: Thirty-seven patients (median age 61.5 years) were enrolled. A total of 140 cycles of chemotherapy were administered (median of 3.8; range 1–8 cycles). Toxicities were evaluated in 36 patients, and the responses were evaluated in 32 patients. Major grade 3/4 toxicities included neutropenia (25%), febrile neutropenia (2.8%), fatigue (22.2%), infection (8.3%), vomiting (5.6%), and mucositis (5.6%). The overall response rate was 12.5% [95% confidence interval (CI), 5.1-28.9%] and disease control rate was 71.9% (95% CI, 56.8-86.3%). The median progression-free survival and overall survival were 3.7 months (95% CI, 2.8-4.6 months) and 6.7 months (95% CI, 3.4-9.9 months), respectively.

Conclusions: The combination of gemcitabine, erlotinib, and S-1 provided an acceptable toxicity profile and modest clinical benefits in patients with advanced pancreatic cancer.

Legal entity responsible for the study: Dae Young Zang

Funding: None

Disclosure: All authors have declared no conflicts of interest.

759P PANOVA: a phase II study of TTFields (150 kHz) with concomitant standard chemotherapy for front-line advanced pancreatic adenocarcinoma: Updated efficacy results

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Background: TTFields are a non-invasive, regional antimitotic treatment modality approved for the treatment of glioblastoma. TTFields act by disrupting mitotic spindle

formation during metaphase. TTFields were effective in preclinical models of pancreatic cancer. PANOVA was the first trial testing TTFields in pancreatic cancer. Results from the first arm of the study, testing TTFields in combination with gemcitabine, have demonstrated superiority in efficacy versus historical controls (J Clin Oncol 34, 2016 (suppl 4S; abstr 269).

Methods: Twenty advanced pancreatic cancer patients were enrolled in the second arm of PANOVA and treated with TTFields in combination with gemcitabine concomitant to nab-paclitaxel. All patients had unresectable tumors, ECOG score of 0-1 and no prior therapy. The primary endpoint was the incidence and severity of adverse events.

Results: The median age was 68.2 (range – 58-81) and most patients (65%) had an ECOG score of 1. Twelve patients (60%) had distant metastases. Ten patients (50%) had serious AEs during the study period. Eleven patients (55%) had treatment-related skin toxicity, of which 5 had grade 3 toxicity. No TTFields-related serious AEs were reported. The median PFS was 12.7 months (95% CI 5.4, NA): 9.3 months in patients with metastatic disease, and not reached in locally-advanced patients. PFS rate at 6 months was 65%: 50% in metastatic disease and 87.5% in locally advanced patients. Of the evaluable tumors, 40% had partial response and another 47% stable disease. The median OS was not reached, and the 1-year survival rate was 72% (62.5% in metastatic disease and 87.5% in locally advanced disease). None of the patients who had a minimal average compliance of 75% died during the follow up period. 87% of the evaluable patients (including all metastatic patients) had a decrease in CA-19-9 levels.

Conclusions: TTFields concomitant to gemcitabine and nab-paclitaxel are safe for advanced pancreatic cancer patients, with promising clinical outcome which doubled historical data. A phase III trial is planned, testing the efficacy of TTFields combined with gemcitabine and nab-paclitaxel in locally-advanced pancreatic cancer patients.

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Legal entity responsible for the study: Novocure

Funding: Novocure

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760P Risk factors for febrile neutropenia (FN) in unresectable/recurrent pancreatic cancer(PC) patients(pts) receiving FOLFIRINOX (FFX) from JASPAC06 study

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Background: FFX is considered one of the standard chemotherapy regimens for chemo-naïve unresectable/recurrent PC pts with good performance status (PS), but can be associated with significant toxicity. A high incidence of FN (22%) was reported from a Japanese phase II trial of FFX. The aim of this study was to clarify the risk factors for FN in these pts.

Methods: We used data obtained from the JASPAC06 study. The subjects were pts with unresectable/recurrent PC who received FFX during one year from Dec. 20, 2013. All the subjects were registered and their clinical data were sent to the data center. The logistic regression model was used to estimate odds ratios (ORs) of the potential risk factors for the development of FN.

Results: A total of 399 pts were included in this analysis. Pts characteristics were: median age 63 years; ECOG-PS 0/1/2, 70/29/1%; disease status locally advanced/metastatic/recurrent, 20/60/20%; prior chemotherapy yes/no, 37/63%; biliary stent before FFX 23%; UGT1A1 polymorphism *28 and *6 wild/single heterozygous/homozygous or double heterozygous, 55/38/4%; Dose reduction at initial treatment yes/no, 68/32%. The median number of treatment cycles was 6. FN occurred in 13% of the pts. A multivariate logistic regression analysis showed that the pretreatment white blood cell count(WBC) $< 4000/\mu L$(OR: 4.29, 95%CI: 1.08 to 15.1, $p = 0.028$), platelet count(Plt) $< 15*10^4/\mu L$ (OR: 2.41, 95% CI: 1 to 5.7, $p = 0.046$), serum total bilirubin(T-Bil) $>$ 1.0mg/dL (OR: 5.83, 95% CI: 2.28 to 14.9, $p = 0.0002$), tumor location in pancreatic head (OR: 2.53, 95%CI: 1.17 to 5.76, $p = 0.022$) and no initial dose reduction (OR: 6.13, 95% CI: 2.81 to 14.4, $p < 0.0001$) were significantly associated with higher risk of FN.

Conclusions: Pretreatment WBC $< 4000/\mu L$, Plt $< 15*10^4/\mu L$, T-Bil > 1.0mg/dL, tumor location and no initial dose reduction might be risk factors for the development of FN in unresectable/recurrent PC pts receiving FFX. The predictive factors proposed in our study could be utilized to select the pts at a high risk for the development of FN who may benefit from dose reduction or G-CSF prophylaxis.

Clinical trial identification: UMIN00014658

Legal entity responsible for the study: JASPAC

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761P A Phase I study of LDE225 in combination with gemcitabine and nab-paclitaxel in patients with metastasized pancreatic cancer

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Background: Metastasized pancreatic cancer has a dismal survival due to poor responses to chemotherapy. Preclinical research suggests that targeting pancreatic tumor stroma with the Sonic Hedgehog inhibitor LDE225 may improve chemotherapy delivery to the tumor.

Methods: We performed a phase IB dose-escalation clinical trial. The primary objectives were to determine the dose-limiting toxicities (DLT), maximum tolerated dose (MTD), and the anti-tumor efficacy of LDE225 in combination with 1000 mg/m^2 gemcitabine and 125 mg/m^2 nab-paclitaxel in patients with metastasized pancreatic cancer. The LDE225 dose was to be escalated, gemcitabine and nab-paclitaxel doses were fixed. Treatment evaluation was performed by CT after 2 cycles of therapy according to RECIST 1.1 criteria. Additional diffusion-weighted MRI scans were performed before and after 2 cycles of treatment.

Results: 26 patients received study treatment for a median duration of 109 days (IQR 54-245) during a median of 4 (IQR 2-8.5) chemotherapeutic cycles. 6 patients discontinued due to toxicity and 20 patients because of progressive disease. At the starting dose level (400 mg LDE225), 1 out of 6 patients experienced a DLT. Because the DLT and most adverse events occurred in patients who received prior chemotherapeutic treatment we divided the cohort in a chemo-naïve ($n = 17$) and a prior-chemo group ($n = 9$). Within the chemo-naive group, the MTD was 800 mg LDE225. In the prior-chemo group, the MTD was 200 mg LDE225. No therapy-related grade 4 adverse events were reported. The most frequent grade 3 reported adverse events were: fatigue (27%), neutropenia (15%) and diarrhea (12%). Of 23 evaluable patients, 6 patients had progressive disease (26%), 8 had stable disease (35%), 8 had a partial response (35%) and 1 patient had a complete response (4%). 12 patients with SD/PR underwent both MRI scans. These patients showed a significant increase in diffusion coefficient after treatment ($1.39 \pm 0.24 \times 10^{-3}$ *vs.* $1.62 \pm 0.25 \times 10^{-3}$ mm^2/s, $P < 0.001$).

Conclusions: The addition of LDE225 to gemcitabine and nab-paclitaxel was well tolerated and showed promising anti-tumor activity, regardless of whether or not patients had received prior chemotherapy for metastatic pancreatic cancer.

Clinical trial identification: EudraCT number 2013-002370-51 NCT02358161

Legal entity responsible for the study: J.W. Wilmink Academic Medical Center Amsterdam - University of Amsterdam (AMC-UvA).

Funding: Academic Medical Center - University of Amsterdam (AMC-UvA) Novartis Pharma BV Cellgene BV.

Disclosure: All authors have declared no conflicts of interest.

762P Impact of advances in systemic chemotherapy for unresectable pancreatic ductal adenocarcinoma (PDAC) in Alberta, Canada

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Background: Since 2011, new systemic therapy combinations, FOLFIRINOX and nab-paclitaxel with gemcitabine, have demonstrated improvements in survival for PDAC. It is unclear if the availability of these therapies have changed referral patterns or the uptake of systemic treatment in the Canadian context, or improved real world outcomes.

Methods: We performed a population-based analysis of patients with a biopsy-proven unresectable/metastatic PDAC from 2009-2016 in Alberta, Canada. The primary outcome was overall survival (OS) of patients who received chemotherapy, pre and post 2011, while controlling for relevant patient and disease characteristics. Secondary outcomes include the proportion of patients referred to a cancer centre, and receipt of systemic treatment in a universal health care system.

Results: A total of 1764 patients with PDAC were identified, with a median age of 70, 51% male, 86% metastatic disease and 59% occurring in the head or neck. 485 patients were diagnosed prior to 2011 while 1279 were diagnosed after. Rates of cancer centre referrals after 2011 increased from 44 to 50% ($p = 0.03$), but there was no difference in the use of initial chemotherapy (26 vs 28%, $p = 0.44$). Use of single agent regimens decreased (81% to 53%) in favour of combination therapy ($p < 0.01$). Specifically FOLFIRNOX changed from (12 to 21%) and nab-paclitaxel (3 to 21%).The median OS of patients pre-2011 who received chemotherapy compared to best supportive care (BSC) was 8.4 vs 1.8 months, and post-2011 7.3 vs 1.6 months, $p < 0.01$. After controlling for age, sex, primary location, stage, chemotherapy use and era, there was no difference in outcomes pre and post 2011, HR 1.057, 95% CI 0.95-1.18, $p = 0.31$, but chemotherapy improved survival compared to BSC, HR 0.32, 95% CI0.28-0.36, $p < 0.01$.

Conclusions: The natural history of PDAC remains very poor, despite advances in systemic therapy. The majority of patients are not receiving systemic chemotherapy, highlighting the need for improvements in diagnosis and referral, even in a universal health care system. There are no modern trials comparing best supportive care to modern chemotherapy, and this population-based study demonstrates a real-world benchmark for improving patient outcomes.

Legal entity responsible for the study: Tom Baker Cancer Centre

Funding: None

Disclosure: R. Lee-Ying: Advisory board: Celgene. W.Y. Cheung: Advisory Celgene: Shire. P. Tang: Advisory Board: Celgene, Shire. All other authors have declared no conflicts of interest.

763P Randomized phase 2 study of PEGPH20 Plus nab-paclitaxel/gemcitabine (PAG) vs AG in patients (Pts) with untreated, metastatic pancreatic ductal adenocarcinoma (mPDA)

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Background: Hyaluronan (HA) accumulation in the tumor microenvironment produces elevated tumor pressure, vascular compression, and reduced drug delivery. PEGPH20 degrades HA, increasing the access and therapeutic index of anticancer agents.

Methods: In Stage 1 of this phase 2 study, pts with untreated mPDA were randomized 1:1 to PAG (P; 3 µg/kg IV 2x/wk x 3 wks in C1, then 1x/wk x 3 wks in C2+, plus AG) vs AG every 28 days. An imbalance in thromboembolic (TE) events in the PAG arm led to a clinical hold (~40% of pts discontinued PEGPH20), exclusion of pts at high risk for TE events and enoxaparin prophylaxis for all pts. In Stage 2, randomization was 2:1 to PAG vs AG. Tumor HA was tested using a novel assay (VENTANA HA RxDx). Primary endpoints were PFS (evaluable pts) and TE event rate (Stage 2). Secondary endpoints were PFS by HA level and ORR.

Results: 279 pts were randomized; 231 are efficacy evaluable. Of 246 pts with HA data, 84 (34%) were HA-High. As of December 16, 2016, the primary PFS endpoint was statistically significant for PAG vs AG (HR 0.73, 95% CI 0.53-1.00; $p = 0.048$) (Table). PFS in HA-High pts was also statistically significant for PAG vs AG (HR 0.51; 95% CI 0.26-1.00; $p = 0.048$). ORR in HA-High pts was 46% (PAG) vs 34% (AG). Overall survival in HA-High pts (exploratory) was 11.5 months (mo) (PAG) and 8.5 mo (AG) (HR 0.96, 95% CI 0.57-1.61). TE events were similar (PAG 14% vs AG 10%) with enoxaparin initiation.

Table: 763P

Population	Events/Total, n Median PFS, months		HR (95% CI)	P value
	PAG	AG		
Efficacy Evaluable (n = 231)	100/139; 6.0	65/92; 5.3	0.73 (0.53, 1.00)	0.048
HA-High (n = 84)	24/49; 9.2	19/35; 5.2	0.51 (0.26-1.00)	0.048

All grade treatment-related AE included peripheral edema (PAG 63% vs AG 26%), muscle spasms (56% vs 3%), neutropenia (34% vs 19%), and myalgia (26% vs 7%).

Conclusions: Randomized Phase 2 study met both primary endpoints (PFS and TE event rate), with the largest improvement in the secondary endpoint of PFS in HA-High pts. These data support HA as a potential predictive biomarker for pt selection of PEGPH20, currently investigated in the global Phase 3 HALO 301 study with PFS and OS as co-primary endpoints. NCT01839487

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Legal entity responsible for the study: Halozyme Therapeutics, Inc.

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764P Crucial relationship of neural wiskott aldrich syndrome protein(N-WASP) and lysyl oxidase-like 2(LOXL2) in the promotion of pancreatic cancer metastasis

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Background: Pancreatic cancer is known to have aggressive malignancy and poor prognosis. N-WASP is part of the WASP family that regulate actin polymerization. FAK (Focal adhesion kinase) promotes N-WASP and epithelial mesenchymal transition(EMT) in cancer metastasis. Previous studies reported the overexpression of LOXL2 activates FAK and Snail and promotes distant metastasis in pancreatic cancer. However, there are few evidence of the relation between LOXL2 and N-WASP. In this study, we aimed to confirm the expression of N-WASP and relationship of N-WASP and LOXL2 in pancreatic cancer.

Methods: Between June 2002 and December 2012, 80 patients underwent curative resection for pancreatic cancer at Gangnam Severance Hospital, Korea. Pancreatic cancer cell lines MIA PaCa-2, PANC-1 were used for in vitro study. We purified the whole RNA and protein to perform the RT-PCR and Western blot. We performed Chromatin immunoprecipitation(ChIP) assay to probe the interaction between Snail and promoter of N-WASP. And we confirmed the motility and invasiveness of MIA PaCa-2 and PANC-1.

Results: Among the 80 patients, 81.2% were positive for LOXL2. On univariate and multivariate analyses, poor differentiation and LOXL2 were identified as prognostic factors for DFS. High expression of LOXL2 and N-WASP were observed and correlated with the expression of mesenchymal markers (Snail, L1CAM, Vimentin). We generated stably LOXL2 silenced pancreatic cancer cell which exhibited significant changes of factors related to invasiveness and N-WASP expression. There were poorly expressions of N-WASP in Snail silencing of same cell lines. In ChIP assay, we obtained the results of the association of Snail proteins with promoter of N-WASP. Silencing of N-WASP decreased motility and invasiveness of MIA PaCa-2 and PANC-1 as determined from wound healing assay.

Conclusions: Our results demonstrated that N-WASP is a regulator of EMT in pancreatic cancer. By identifying of N-WASP expression promoted by Snail, LOXL2 and N-WASP have a powerful relationship for activating the promotion of EMT in pancreatic cancer metastasis. These findings suggest that N-WASP can be a target for the determining of distant metastasis in pancreatic cancer.

Legal entity responsible for the study: Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Korea Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Korea. Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Korea. Gangnam Severance Hospital, Yonsei University College of Medicine

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765P The nationwide cancer genome screening project in Japan SCRUM-Japan GI-SCREEN: Efficient identification of cancer genome alterations in advanced small intestine cancer

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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.

Methods: This study is ongoing with 20 major cancer centers. Patients with aNon-CRC, including who plan to or receive chemotherapy were eligible. DNA and RNA were extracted from FFPE tumor samples and were analyzed by the Oncomine Cancer Research Panel (OCP) which allows to detect gene mutations, copy number variants (CNVs) and gene fusions across 143 genes in a CLIA certified CAP accredited laboratory. 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. In this presentation, we show the results of advanced small intestine cancer cohort.

Results: As of October 31st in 2016, a total of 36 advanced small intestine cancer samples were analyzed. The sequence was successfully performed in 26 tumors (72.2%). Out of 26 patients, the primary tumors are located in duodenum ($n = 15$), jejunum ($n = 7$), and ileum ($n = 2$), and unknown ($n = 2$). The frequently detected mutations in 26 samples of which results were available were *KRAS* (50.0%), *TP53* (42.3%), and *APC* (23.1%). The frequently detected CNVs ($\geq$ 7copies) were *MDM2* (7.7%) and *CDK6* (3.8%). *PIK3CA* mutations were identified in 4 cases (15.4%) and *BRAF* mutations were identified in 2 cases (7.7%). No gene fusion was detected.

Conclusions: This nationwide screening system is efficient to detect rare gene alterations in advanced small intestine cancer. This novel knowledge provides an intriguing background to investigate new target approaches and represents a progress toward more 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: W. Okamoto: Research Funding from MSD. Y. Honma: Honoraria from Tenjin pharma. Speakers' bureau from Taiho, Nihon kayaku, Daiichi sankyo and Novartis. Research funding from Daiichi Sankyo, Astrazeneca, Merck serono, Novartis and Teijin pharma. T. Kudo: Research funding from Yakult Honsha, Chugai Pharma and Ono Pharma. Y. Komatsu: Honoraria from Novartis, Pfizer and Bayer. Speakers' bureau from Taiho, Lilly, Chugai, Merch, Novartis, Pfizer and Bayer. Research funding from Taiho, Lilly, MSD, Ono, Novartis, Bayer, Chugai and Yakult. H. Hara: Honoraria from Chugai, Taiho, Merck Serono, Yakult and Lilly. Consulting or advisory role from Ono and Chugai. Research funding from AstraZeneca, Chugai, Merck Serono, MSD, Ono, Taiho, Takeda, Boehringer Ingelheim, Daiichi Sankyo, Lilly, etc. D. Naruge: Research funding from Taiho, Ono, Onco Therapy Science, Merck, Zeria, Lilly, Takeda, Chugai, Bayer, Graxo Smith Kline, Yakult, Sumitomo Dainippom, Daiichi Sankyo, Novartis, Bristol-Myers, Sanofy, Kyowa Hakko Kirin, Astellas, Pfizer, Janssen. T. Moriwaki: Honoraria from Bayer, Chugai Pharma, Merck Serono, Novelpharma, Taiho Pharmaceutical, Takeda, and Yakult Honsha. Research funding from Boehringer Ingelheim, Chugai Pharma, MSD Oncology, Sanofi-Aventis, Taiho Pharmaceutical, Takeda, and Yakult Honsha. S. Nomura: An immediate family member has been employed by Asahi-Kasei pharma. K. Shitara: Receipt of grant/research supports from Daiichi Sankyo, Chugai Pharma, Lilly, MSD, Taiho Pharmaceutical and Dainippon Sumitomo Pharma. A. Ohtsu: An immediate family member has been employed from Celgene. Research Funding from Bristol-Myers Squibb. T. Yoshino: Research funding from GlaxoSmithKline K.K. and Boehringer Ingelheim GmbH. All other authors have declared no conflicts of interest.

766P Frequent ERBB3 (HER3) activating mutations in small bowel adenocarcinomas

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Background: Functional studies have demonstrated that mutations of the ERBB3 oncogene, which encodes the HER3 receptor, are oncogenic through the activation of the HER2 signalling pathway (Jaiswal et al, Cancer Cell 2013). We and other have reported a significant clinical activity of anti-HER2 therapy in patients with ERBB3-mutated cancers (trastuzumab/lapatinib combination: Bidard et al, Ann Oncol 2015; afatinib: Choudury et al, JCO 2016). This study aimed at reporting the rate of activating ERBB3 mutations in small bowel adenocarcinoma (SBC), a rare tumor type in which we previously reported a high rate (12%) of activating ERBB2 mutations (Laforest et al, Eur J Cancer 2014).

Methods: DNA from 74 SBC, which have been previously characterized for ERBB2 mutations and MSI status, were subjected to HRM analysis followed by Sanger sequencing of ERBB3 exons 3, 6, 7, 8 and 23. Orthogonal validation by targeted NGS was performed for two patients (HiSeq, 50 genes, mean depth 10000x)

Results: 4 of the 74 SBC (5.4%) displayed activating *ERBB3* mutations, including 3 p.V104M mutations (c.310 G>A) in exon 3 and 1 p.E928G mutation (c.2783 A>G) in exon 23. No mutation was detected in exon 6, 7 and 8. Activating *ERBB3* mutations were associated with microsatellite instability ($p = 0.002$) and with the presence of activating *ERBB2* mutations ($p = 0.002$). 2 SBC cases with a co-occurrence of *ERBB2* and *ERBB3* mutations were further analyzed by targeted NGS: in addition to confirming the co-occurence of these activating mutations, mutant allelic frequencies did not suggest a subclonal distribution: 24.3% (*ERBB3* p.V104M) vs 25.9% (*ERBB2* p.L755S) and 18.5% (*ERBB3* p.V104M) vs 24.5% (*ERBB2* p.L755S) vs 20.6% (*BRCA2* p.Q1782fs) in the first and second case, respectively.

Conclusions: SBC display a high rate of *ERBB3* activating mutations, which have been shown to be targetable by anti-HER2 therapies. Strikingly, in most cases, *ERBB3* was co-mutated with *ERBB2*, suggesting a strong oncogenic addiction of these SBC to the HER2 pathway.

Legal entity responsible for the study: Luc Cabel

Funding: None

Disclosure: All authors have declared no conflicts of interest.

767TiP CLASS-05 trial: A randomized controlled phase III trial of cytoreductive surgery + hyperthermic intraperitoneal chemotherapy (HIPEC) + systemic chemotherapy vesus systemic chemotherapy alone for patients with limited peritoneal carcinomatosis of gastric cancer

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Background: Peritoneal metastasis (PM) is detected synchronously in ~30% of patients with advanced gastric cancer (AGC), which has been considered as late stage of the disease with a poor prognosis and were generally treated with systemic chemotherapy or best supportive care. Two new surgical modalities that have evolved to manage PM are cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC). Our and other published retrospective data suggested that CRS plus HIPEC may prolong overall survival of the patients with limited PM. Still, the solid evidences based on large randomized clinical trials (RCT) are lacking. Accordingly, the present trial was initiated to define a comprehensive treatment.

Trial design: The investigator-initiated, multicenter, prospective two-arm RCT is comparing efficacy of CRS followed by HIPEC (CRS+HIPEC) versus chemotherapy (5-Fu based regimen, Chemo) alone for the treatment of AGC with limited PM. Eligibility for the trial is given in cT3-4NxM1 (M1 limited to peritoneum, PCI score < 20 evaluated by diagnostic laparoscopy)AGC. The trial will recruit 220 participants who are 1:1 randomized to one of two arms after diagnostic laparoscopy. Participants enrolled in the Chemo study arm will receive standard chemotherapy according to the NCCN guideline. The CRS+HIPEC study arm will receive D2 gastrectomy plus peritonectomy plus HIPEC followed by systemic chemotherapy. The primary endpoint of the trial is overall survival. The secondary endpoints include progression-free survival, morbidity and mortality and quality of life. Biological substudies on biomarkers are included. Current status: The trial was approved by the Ethical Committee of Nanfang hospital, Southern Medical University, Guangzhou, China. Patient recruitment has begun in January 2017. Overall 12 Chinese sites will commence recruitment in 2017.

Clinical trial identification: NCT03023436

Legal entity responsible for the study: Nanfang Hospital, Southern Medical University

Funding: None

Disclosure: All authors have declared no conflicts of interest.

768TiP A prospective multicenter, phase II trial (NAC-GA trial) to evaluate the effect of neoadjuvant nab-paclitaxel plus gemcitabine therapy on overall survival in patients with borderline resectable pancreatic cancer

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Background: Overall survival after neoadjuvant therapy and surgery for Borderline resectable pancreatic carcinoma (BRPC) is recognized as a goal for a multidisciplinary approach.

Trial design: Objective: The NAC-GA trial was a prospective multicenter phase II trial and its implementation was planned for patients with BRPC defined as borderline by the National Comprehensive Cancer Network (Version 2.2016) to investigate improvement of overall survival after the first day of initial therapy. Endpoints: This clinical trial primarily evaluated the primary endpoint of overall survival time from the first day of protocol therapy. The secondary endpoints were recurrence-free survival from the first day of protocol therapy, safety of the protocol therapy (adverse effects), morbidity, response rate, disease control rate, preoperative/postoperative tumor marker (CA19-9, CEA), rate of normalization, reduction rate of SUVmax value on PET-CT, chemotherapeutic effect, resection rate, R0 resection rate, surgical data, overall morbidity rates, rate of patient undergo postoperative adjuvant therapy, dose intensity, quality of life regarding fatigue and malaise assessed by the questionnaire of FACIT-F, and peripheral sensory neuropathy (PSN) assessed by the questionnaire of FACT/GOG-NTX subscale (Version 4) and Patient Neurotoxicity Questionnaire (PNQ). Sixty patients were included in the study. Treatment Methods: Enrolled patients were administered a 30-min intravenous infusion of nab-paclitaxel at a dose of 125 mg/m^2, followed by a 30-min intravenous infusion of gemcitabine at a dose of 1000 mg/m^2, on days 1, 8 and 15 over a four-week period as one cycle of regimen. Even if the dose on day 8 was missed, the next dose was still administered on day 8 of the same cycle as originally scheduled. All patients were given one week of rest between two cycles. This regimen was repeated twice. In the absence of disease progression, patients would undergo planned pancreatectomy within eight weeks. Postoperative adjuvant therapy was unregulated in this study.

Clinical trial identification: UMIN Clinical Trials Registry (UMIN000024154) - ClinicalTrials.gov (NCT02926183)

Legal entity responsible for the study: Wakayama Medical University

Funding: Research fund was provided to the Wakayama Medical University by Taiho Pharmaceutical Co., Ltd, Tokyo, Japan under a research agreement.

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769TiP Randomized phase II study of modified FOLFIRINOX versus gemcitabine plus nab-paclitaxel combination therapy for locally advanced pancreatic cancer: Japan Clinical Oncology Group Study (JCOG1407)

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Background: Gemcitabine (GEM) is a standard treatment for locally advanced pancreatic cancer (LAPC), but the prognosis is still poor. FOLFIRINOX and GEM plus nab-paclitaxel (GnP) have recently shown superior efficacy over GEM in patients (pts) with metastatic disease, and may also benefit LAPC pts. In addition, phase II study of modified FOLFIRINOX (mFOLFIRINOX), in which dose of irinotecan was reduced and bolus 5-FU was omitted, conducted in Japan showed comparable efficacy with original regimen and tolerable toxicity. The aim of this study is to evaluate the efficacy and safety of mFOLFIRINOX and GnP to determine which is more promising regimen for LAPC. Another aim of this study is to compare the selected regimen with historical control of GEM to determine which should be a standard therapy for LAPC.

Trial design: Chemotherapy-naïve pts with LAPC, an ECOG PS of 0–1, aged 20-75, and adequate organ function are randomized to mFOLFIRINOX or GnP. In the mFOLFIRINOX arm, 85 mg/m^2 of oxaliplatin, 200 mg/m^2 of l-leucovorin, 150 mg/m^2 of irinotecan, followed by 2,400 mg/m^2 of continuous 5-FU over 46 hours are infused every 2 weeks. In the GnP arm, 125 mg/m^2 of nab-paclitaxel followed by 1,000 mg/m^2 of gemcitabine are infused on days 1, 8, and 15 every 4 weeks. Both treatments are continued until disease progression or unacceptable toxicity. The primary endpoint is 1-year overall survival (OS). To select the more effective regimen in 1-year OS (53% vs $\geq$ 63%), 106 pts are needed with a probability of at least 0.85. After selecting the more promising regimen, to judge that regimen replaces GEM as a standard chemotherapy for LAPC, 120 pts are needed to maintain 80% power under the hypothesis of 1-year OS as the expected value of 70% and threshold value of 53% with one-sided alpha of 5%. The planned total sample size is 124 pts considering for a few ineligible pts and lost to follow-up. The planned accrual period is 2.5 years, and the follow-up period is 1 year for primary analysis. Thirty-six institutions are participating in this study. This study was activated in July 2016 and 24 pts were enrolled as of Apr 30, 2017.

Clinical trial identification: UMIN000023143

Legal entity responsible for the study: Japan Clinical Oncology Group

Funding: MHLW, Japan and Japan AMED

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770TiP NIFE-trial: Liposomal irinotecan (nal-IRI) plus 5-fluorouracil (5-FU) and leucovorin (LV) or gemcitabine plus cisplatin in advanced biliary-tract cancer: An open label, randomized, multicenter phase II trial of the AIO

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Background: Biliary tract cancer (CCC) is associated with a poor prognosis due to mostly advanced stages at diagnosis. Overall survival does not exceed 6 months and the 5-year overall survival rate is less than 5% for patients with advanced or metastatic disease. Advanced CCC shows response to chemotherapy resulting in an improved disease control, improved survival and quality of life (QoL). In the ABC-02 phase III trial, gemcitabine combined with cisplatin compared with gemcitabine alone prolonged PFS (8.0 vs. 5.0 mo) and OS (11.7 vs. 8.1 mo) and is considered as standard of care. So far this regimen has not been compared with other active combination regimen. Irinotecan in combination with 5-FU showed promising results in 1st- and 2nd-line therapy in many GI cancers. In pancreatic adenocarcinomas, the combination of liposomal irinotecan (nal-IRI) plus 5-FU/LV improves survival in a post gemcitabine-based treatment setting. Our research hypothesis is that this regimen compares well with respect to clinical endpoints with the standard of care gemcitabine plus cisplatin in patients with advanced CCC.

Trial design: NIFE is a randomized study for patients (to be enrolled: n = 92) with locally advanced or metastatic, non-resectable, adenocarcinoma of the biliary tract: Arm A (experimental): Nal-IRI 80 mg/m2, leucovorin 400 mg/m2, 5-FU 2400 mg/m2, on day 1, cycle q2w), Arm B (standard): Cisplatin 25 mg/m2 and Gemcitabine 1000 mg/m2 on day 1 and 8, cycle q3w. NIFE is an open label, non-comparative, multicenter, two-sided phase II study with an unconnected analysis of the results in both arms against a fixed PFS rate (< 40% at 6 months). The randomization (1:1) is eminent to achieve two comparable patient groups. Primary objective is PFS at 6 months. Key secondary objectives are 3-year OS, PFS, ORR, DCR and QoL/TUDD. There will be a retrospective central surgical and radiological review. Tissue and blood sample collection will be mandatory for biomarker analyses (microdissection and exome sequencing of tumor tissue, ctDNA exome sequencing, transcriptome, miRNA-arrays). Start was in II/2017 in 25 centers in Germany.

Clinical trial identification: NCT03044587, January 23, 2017

Legal entity responsible for the study: AIO Studien gGmbH

Funding: Baxalta/Shire

Disclosure: T.J. Ettrich: The Trial is sponsored by Baxalta/Shire. Thomas Ettrich was member of an Baxalta/Shire advisory board in 2016. All other authors have declared no conflicts of interest.

771TiP A feasibility study of TAS-118 plus oxaliplatin as perioperative chemotherapy for locally advanced gastric cancer

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Background: TAS-118 is a novel combination antitumor agent, which the components of S-1, i.e. tegafur (FT), gimeracil (CDHP), and oteracil potassium (Oxo), are combined with calcium folinate (LV) into one granular form. In a phase II study, S-1 plus LV and oxaliplatin was more active than S-1 plus LV or S-1 plus cisplatin with acceptable toxicities for patients with advanced gastric cancer. A phase 3 study comparing TAS-118 plus oxaliplatin with S-1 plus cisplatin in advanced gastric cancer is in progress in Japan and Korea (NCT02322593). This study is designed to assess feasibility of preoperative adjuvant chemotherapy with TAS-118 plus Oxaliplatin, and postoperative adjuvant therapy with TAS-118 alone or TAS-118 plus Oxaliplatin, in patients with resectable locally advanced gastric cancer with lymph node metastasis.

Trial design: Histopathologically confirmed locally advanced gastric cancer pts with cT3-4N1-3M0 on image findings (Japanese Classification of Gastric Carcinoma, 14th Edition) with no distant matastasis, aged 20 to 79 years, are enrolled in this study. Eligible pts will receive the regimen consists of 3 parts: i) preoperative 4 courses of TAS-118(80-120mg/body; day1-7) plus Oxaliplatin (85mg/m^2; day1) every two weeks ii) gastrectomy with D2 lymphadenectomy iii) postoperative 12 courses of TAS-118 alone(80-120mg/body;day1-7) (step1) or 8 cycles of TAS-118 plus Oxaliplatin(step2); every two weeks . The primary endpoints are feasibility of i) preoperative adjuvant chemotherapy with TAS-118 plus Oxaliplatin and gastrectomy, ii) postoperative adjuvant chemotherapy with TAS-118 alone(step1) and TAS-118 plus Oxaliplatin(step2). The target sample size is 45. Secondary endpoints include the treatment completion rate of chemotherapy and surgery, relative dose intensity, clinical and pathological response rates for preoperative chemotherapy, R0 resection rate, down staging rate, relapse free and overall survival, and safety. This IIT study is conducted in 3 sites in Japan and has initiated from November 2016.

Clinical trial identification: UMIN000024688 release date: 5 Dec 2016

Legal entity responsible for the study: Kensei Yamaguchi

Funding: Taiho, Yakult

Disclosure: A. Takashima: Speaker's bureau: Takeda, Chugai, Taiho, Merk Serono. Research funding: Chugai, Taiho, Merk Serono, Gilead. D. Takahari: Research funding: Taiho Honoraria: Taiho, Yakult, Lilly, Chugai. N. Ishizuka: Stock ownership: Sanofi Honoraria: Daiichi-Sankyo Adovisory role: BMS. T.E. Nakajima: Honoraria: Taiho, Eli Lilly, Chugai, Kyowa Hakko Kirin, Hisamitsu, Merck Serono, Sawai, Takeda, Bristol-Myers Squibb, Ono, Bayer, Dainippon Sumitomo. Research funding: Taiho, Eli Lilly, Chugai, Kyowa Hakko Kirin, Hisamitsu, Merck Serono, Sawai, Takeda. S. Takahashi: Honoraria: Eisai, Astellas, Taiho, Bayer, Daiichi-Sankyo, Pfizer, Astrazeneca, Merck Serono, Sanofi, Novartis, Ono, Bristol-Myers, MSD. Research funding: Eisai, Chugai, MSD, Lilly, Astrazeneca, Novartis, Taiho, Bayer, Astellas, Ono, Daiichisankyo. T. Sano: Honoraria: Taiho, Chugai, Yakult, Lilly, Eisai, Ethicon, Covidien. N. Boku: Honoraria: Lilly, Taiho, Chugai, Ono, Merck-Serono, Yakult. Research funding: Ono, Bristol-Myers Squibb, Taiho. K. Yamaguchi: Speaker's bureau: Takeda, Lilly, Taiho, Chugai, Merck. Research funding: Yakult, Taiho, MSD, Ono, Chugai, Lilly, Merck. All other authors have declared no conflicts of interest.

772TiP A phase 1/2 study of ramucirumab plus nivolumab in patients with previously treated advanced gastric adenocarcinoma

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Background: Nivolumab (Nivo) is a human IgG4 programmed death receptor-1 (PD-1) monoclonal antibody that blocks the interaction between PD-1 and its ligands, releasing PD-1 pathway-mediated inhibition of the anti-tumor immune response. Nivo has demonstrated significant improvement in overall survival (OS) in the phase III trial (ONO4538-12) for patients (pts) in salvage line treatment of advanced gastric cancer (AGC). Ramucirumab (Ram) is a human IgG1 monoclonal VEGFR-2 antagonist antibody. Ram as monotherapy or in combination with paclitaxel, prolonged survival in AGC. Blocking VEGFR-2 relieves T cell exhaustion by reverting the expression of inhibitory molecules, and improves T cell infiltration into tumors. Based on synergistic anti-tumor effect induced by simultaneous blockades of PD-1 and VEGFR-2 in preclinical studies, this phase I/II study is designed to investigate the safety and tolerability of Nivo plus Ram in the 2nd line chemotherapy for with AGC. This study is conducted at 5 sites in Japan and started in January 2017.

Trial design: AGC pts with measurable lesions, aged $\geq$ 20 years, after disease progression on 1st line chemotherapy (platinum plus fluoropryimidine) will be enrolled in this study. Eligible pts will receive Ram and Nivo every two weeks until unacceptable toxicity or disease progression. In the phase I part, the doses of Ram/Nivo will set at 8/3 mg/kg (level 1) and 8/1 (level 0), and the recommended dose (RD) of Ram and Nivo will be determined based on the safety of 6 patients. In the phase II part, the primary endpoint is a 6-months progression-free survival (PFS) rate. The planned sample size is 44 with one-sided alpha of 0.05 and power of 80% based on the expected and threshold 6-months PFS ratios as 36% and 18% (using the Kaplan–Meier estimator). Secondary endpoints include overall response rate, disease control rate, overall survival, and safety. Exploratory endpoints include anti-tumor immune response using immune gene expression, PD-L1 and mismatch repair protein expression in tumor tissue, immune cell subset in peripheral blood, serum drug concentration measurements, serum microRNA expression, and genomic profiling of CTCs using next-generation sequencing, etc. Clinical trial information: NCT02999295

Clinical trial identification: NCT02999295

Legal entity responsible for the study: Ken Kato

Funding: Ono Pharmaceutical

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773TiP PRODIGE 51 - GASTFOX: Phase III randomised trial evaluating FOLFOX with or without DOCETAXEL (TFOX) as 1st line chemotherapy for locally advanced or metastatic oesophago-gastric adenocarcinoma

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Background: In advanced gastric cancer, doublet regimen with cisplatin and fluoropyrimidine is considered as a 1st-line standard treatment (trt). Taxane is also effective in 2nd line. The addition of docetaxel (75 mg/m^2) to cisplatin (75 mg/m^2) and 5-fluorouracil ("DCF regimen") every 3 weeks has been shown to improve efficacy of 1st-line trt in a phase III trial. However, this regimen was associated with more frequent grade 3-4 toxicities, such as diarrhea, neutropenia and complicated neutropenia (febrile neutropenia or neutropenic infection). Oxaliplatin has been shown to be more tolerable than cisplatin with the same efficacy. The addition of docetaxel at 50 mg/m^2 every 2 weeks to the FOLFOX (TFOX regimen) showed to be active and tolerable in phase II studies and less toxic as compared DCF regimen. The aim of this current phase III study is to compare FOLFOX to TFOX in 1st line trt of advanced gastric cancer.

Trial design: The major eligibility criteria are: Patient $\geq$ 18 years, WHO PS $\leq$ 1, with histological proven gastric or gastro-oesophageal junction HER2 negative adenocarcinoma, metastatic or locally advanced measurable disease (RECIST v1.1 criteria). Trt is administered every 14 days.

Table: 773TiP

	FOLFOX (BRAS A)	TFOX (BRAS B)
Folinic acid (D1)	400 mg/m^2	400 mg/m^2
Oxaliplatin (D1)	85 mg/m^2	85 mg/m^2
5FU bolus (D1)	400 mg/m^2	
5FU continu (D1-2)	2400 mg/m^2	2400 mg/m^2
Docétaxel (D1)		50 mg/m^2

Trt has to be administrated until disease progression or unacceptable toxicity. The primary criterion is radiological/clinical progression-free survival (PFS). A difference of 2 months for the median PFS in favor of TFOX is expected (5.5 months in FOLFOX arm vs 7.5 months in TFOX arm), HR = 0.73. (α = 5%, power of 90%, O'Brien – Fleming function). An interim analysis is planned at 227 events (progression or death) for early efficacy or futility search. Secondary criteria are: overall survival, objective response rate, therapeutic index, toxicity, time to final deterioration in quality of life. Stratification factors are: centre, WHO PS, adjuvant chemotherapy or radio-chemotherapy, tumour stage, primary tumour location and pathological subtype. 17 patients have been randomized over the 506 planned since 19/12/2016.

Clinical trial identification: EudraCT n° 2016-002331-16; NCT03006432

Legal entity responsible for the study: FFCD

Funding: None

Disclosure: A. Zaanan: Consulting and/or advisory board for Roche, Merck Serono, Amgen, Sanofi, Lilly. E. Samalin: Personal grants for consultancy for Sanofi, Lilly, Novartis, Bayer, Roche, Ipsen, Amgen, Merck. F. Khemissa: Personal grants for consultancy for Sanofi, Roche, Ipsen, Bayer. O. Bouche: Personal grants for consultancy for Roche, Merck, Amgen, Lilly, Novartis Oncologie. F. Ghiringhelli: Personal grants for consultancy for Amgen and Merck. B. Chibaudel: Consulting: Sanofi, Lilly. Honoraria: Bayer, Kephren, Kantar H. Travels: Roche, Sanofi, Amgen, Merck, Lilly. Y. Molin: Regional board for Janssen. O. Romano: Roche, Pierre Fabre, Sanofi. T. Aparicio: Personal grants for consultancy for Amgen, Roche, Bayer, Pierre Fabre, Novartis Oncologie, Pfizer, Sanofi, Vifor Pharma, Ipsen Pharma. P. Michel: Personal grants for consultancy for Sanofi, Lilly. J. Taieb: Personal grants for consultancy for Amgen, Baxalta, Celgene, Lilly, Merck, Msd, Pfizer, Roche, Sanofi, Abbvie. All other authors have declared no conflicts of interest.

774TiP Global phase 3, randomized, double-blind, placebo-controlled study evaluating PEGylated recombinant human hyaluronidase PH20 (PEGPH20) plus nab-paclitaxel and gemcitabine in patients with previously untreated, hyaluronan (HA)-high, stage IV pancreatic ductal adenocarcinoma (PDA)

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Background: Poor outcome in PDA is associated with stromal hyaluronan (HA) accumulation, which may compromise treatment access. In animal models, PEGPH20 degrades tumor HA. Key data from a Phase 2 study showed that PEGPH20 plus chemotherapy improved efficacy over chemotherapy alone in tumors retrospectively identified to accumulate HA ("HA-High"). The objectives of this Phase 3 study are to compare efficacy and safety of standard-dose nab-paclitaxel (NAB) and gemcitabine (GEM) combined with PEGPH20 or placebo in patients with HA-High, previously untreated, Stage IV PDA. Primary endpoints are progression-free survival (PFS) and overall survival (OS). Secondary endpoints are objective response rate, duration of response, and safety.

Trial design: 420 patients $\geq$18 years with untreated HA-High metastatic PDA, ECOG PS 0-1 are randomized (stratified by North America/Europe/Other) 2:1 to NAB 125 mg/m^2 + GEM 1000 mg/m^2 + PEGPH20 3.0 µg/kg or to NAB + GEM + placebo, respectively. Patients with HA-High tumors are prospectively identified by the co-developed VENTANA HA RxDx Assay, which identifies HA in the extracellular matrix. HA-High status (indicating patients who may achieve clinical benefit) was determined by Halozyme to be $\geq$ 50% HA staining based on clinical outcome data from a Phase 2 study. Treatment is provided in 4-week cycles (Wk 1-3, Wk 4 rest) until disease progression, unacceptable toxicity, death, or consent withdrawal. PEGPH20 or placebo is given twice weekly (Cycle 1) then weekly (Cycles 2+), NAB + GEM once weekly for all cycles. Dexamethasone is given before and after PEGPH20 to reduce treatment-related musculoskeletal symptoms and enoxaparin is given to minimize thromboembolic events. Tumor response will be assessed by an independent central imaging vendor using RECIST v1.1. Adverse events will be graded per NCI CTCAE v4.03. An independent Data Monitoring Committee will evaluate safety and efficacy (PFS and OS) data. Trial initiated Q12016 (EudraCT 2015-004068-13; NCT02715804).

Clinical trial identification: NCT02715804

Legal entity responsible for the study: Halozyme Therapeutics, Inc.

Funding: Halozyme Therapeutics, Inc.

Disclosure: E. Van Cutsem: Research funding: Halozyme. A. Hendifar: Consulting or Advisory Role: Genentech, Novartis, Ipsen, Perthera Travel, Accommodations, Expenses: Halozyme. M. Reni: Grant: Celgene, Baxalta, Merck-Serono, Helsinn Personal fee: Celgene, Baxalta, Merck-Serono, Boheringer, Lilly, Pfizer, AstraZeneca, Novocure, Genentech, Halozyme Non-fin support: Celgene. L. Zheng: Consult/Advisory:Merrimack Patents/royal: GVAX,Licensed to Aduro Biotech Stock/Other: Z&L Medical Intl Res Fund: BMyers Squibb,Amgen, Iteos Therap,Gradalis,Merck,Halozyme. M. Ducreaux: Honoraria: Roche,Celgene,Merck Serono,Amgen,Novartis,Sanofi,Pfizer,Lilly,Servier, Halozyme Grants/ResFund: Roche,

Chugai, Pfizer Spouse: Head of BU, Sandoz. W. Harris: Consulting or Advisory Role: Neotherma Oncology, Bayer Research Funding: Halozyme, BMS, Exelixis, Argule, Polaris, Medimmune, BTG. P. Corrie: Honor: Roche, Novartis, BM Squibb, Merck Sharpe&Dohme,Pierre Fabre Res fund: Celgene Ad hoc honor for lectures/mtg present: Novartis, Celgene,Merck Sharpe & Dohme. T. Seery: Consulting or Advisory Role: Bayer Speakers' Bureau: Ipsen, Bayer. D. Chondros: Halozyme employee. A. Bullock: Consulting or advisory board participation support: Halozyme, Celgene, and EMD Serono.

775TiP KEYNOTE-240: Phase 3, randomized study of pembrolizumab (pembro) vs best supportive care (BSC) for second-line advanced hepatocellular carcinoma (HCC)

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Background: Sorafenib is the standard of care (SOC) for first-line HCC; however, there is no clear SOC after disease progression on or intolerance to sorafenib. Because most HCC is driven by inflammation, the rationale to evaluate immunotherapy in patients (pts) with this type of cancer is strong. The randomized, double-blind, placebo-controlled phase 3 KEYNOTE-240 study (ClinicalTrials.gov, NCT02702401) was designed to compare efficacy and safety of the anti–PD-1 antibody pembro + BSC vs placebo + BSC in pts with previously treated advanced HCC.

Trial design: Pts aged ≥18 years with histologically or cytologically confirmed HCC (fibrolamellar and mixed hepatocellular/cholangiocarcinoma subtypes excluded), documented progression after stopping treatment with sorafenib or intolerance to sorafenib, no previous systemic therapy for HCC other than sorafenib, disease not amenable to a curative treatment approach (eg, transplantation, surgery, or ablation), measurable disease confirmed by central imaging vendor review per RECIST v1.1, Child-Pugh liver score A, ECOG performance status 0-1, adequate organ function, and predicted life expectancy >3 months are eligible. Pts will be randomly assigned 2:1 to receive pembro 200 mg IV Q3W + BSC or placebo Q3W + BSC for up to 35 cycles (~2 years) or until disease progression, unacceptable toxicity, or investigator decision. Randomization will be stratified by geographic region, presence of macrovascular invasion, and α-fetoprotein level. BSC will be provided by the investigator per local treatment practices. Response will be assessed Q6W per RECIST v1.1 by central imaging vendor review. Adverse events (AEs) will be assessed throughout treatment and for 30 days thereafter (90 days for serious AEs) and graded per NCI CTCAE v4.0. Primary objectives are comparison of PFS per RECIST v1.1 by central imaging vendor review and OS between treatment arms. Secondary objectives are comparison of ORR, DOR, DCR, and TTP per RECIST v1.1 by central imaging vendor review, and evaluation of safety and tolerability. Planned enrollment in KEYNOTE-240 is 408 pts across 26 countries.

Clinical trial identification: NCT0270240, March 3, 2016

Legal entity responsible for the study: Merck & Co., Inc., Kenilworth, New Jersey, USA

Funding: Merck & Co., Inc., Kenilworth, New Jersey, USA

Disclosure: R.S. Finn: Consulting/advisory role: Bayer, Novartis, Pfizer, BMS, Merck; Research funding: Bayer (to institution). S.L. Chan: Consulting/advisory role: Medimmune, Novartis. A.X. Zhu: Consulting/advisory role: Merck. J. Knox: Consulting/advisory role: Merck; Research funding: AstraZeneca. A-L. Cheng: Consulting/advisory role: Novartis, Merck Serono, Eisai, Merck, Sharp & Dohme, Ono, BMS, Bayer. A.B. Siegel: Employment and stock: Merck. O. Bautista: Employment and stock: Merck & Co., Inc. M. Kudo: Honoraria: Bayer, Eisai, MSD, Ajinomoto; Research funding: Chugai, Otsuka, Takeda, Taiho, Sumitomo Dainippon, Daiichi Sankyo, MSD, Eisai, Bayer, Abbvie.

776TiP PACTO: A single center, randomized, phase II study of the combination of nab-paclitaxel and gemcitabine with or without tocilizumab, an IL-6R inhibitor, as first-line treatment in patients with locally advanced or metastatic pancreatic cancer

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Background: High plasma levels of interleukin-6 (IL-6) are found in patients with pancreatic cancer (PC) and in part facilitate systemic inflammation cascade and cachexia. The current phase 2 trial (PACTO) will evaluate the efficacy and safety of *nab*-paclitaxel and gemcitabine with or without tocilizumab, an IL-6R inhibitor, as first-line treatment in patients with advanced PC.

Trial design: Eligible patients with chemotherapy-naïve locally advanced or metastatic PC (n = 140), ECOG performance status (PS) of 0–1, and presence of a systemic inflammatory response (elevated C-reactive protein [CRP] levels or a modified Glasgow Prognostic Score [mGPS] of 1 or 2) will be randomized 1:1 (stratified by PS [PS 0 vs PS 1] and stage [locally advanced vs metastatic disease]) to receive tocilizumab 8 mg/kg on day 1 in combination with nab-paclitaxel 125 mg/m2 plus gemcitabine 1000 mg/m2 or nab-paclitaxel 125 mg/m2 plus gemcitabine 1000 mg/m2 on days 1, 8, and 15 of a 28-day cycle. Before randomization begins, the first six patients enrolled will be treated in the investigational arm for safety assessment and will not be included in the final analysis. The primary endpoint is overall survival (OS) rate at 6 months. Assuming a 6 month OS rate of 67% in the reference arm and an improvement by at least 20% by the intervention (corresponding to a 6 month OS of 80%), a total of 140 patients are needed (1:1 allocation) to obtain a statistical power of 80% with a significance level of 5%. Secondary endpoints include change from baseline PS, assessed by both investigator and patient, progression-free survival, OS, tumor response per RECIST 1.1, safety and assessment of quality of life by EORTC QLQ-C30. Patients will be assessed by CT scan every 8 weeks. Exploratory endpoints include circulating tumor DNA KRAS, body composition changes, plasma biomarkers of cachexia and inflammation. Treatment will continue as long as it is tolerated until disease progression. Enrollment was initiated in January 2017 and is ongoing.

Clinical trial identification: NCT02866383

Legal entity responsible for the study: Herlev & Gentofte Hospital

Funding: Celgene

Disclosure: All authors have declared no conflicts of interest.

777TiP ATTRACTION-04 (ONO-4538-37): A randomized, multicenter, phase 2/3 study of nivolumab (Nivo) plus chemotherapy in patients (Pts) with previously untreated advanced or recurrent gastric (G) or gastroesophageal junction (GEJ) cancer

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Background: Nivo, a fully human IgG4 programmed death 1 (PD-1) immune checkpoint inhibitor, has demonstrated survival benefits across a number of tumor types. In ATTRACTION-02 (ONO-4538-12), a double-blind, placebo-controlled, Phase 3 study in pts with unresectable advanced or recurrent G/GEJ cancer refractory to or intolerant of standard therapy, Nivo monotherapy (3 mg/kg Q2W) demonstrated survival benefits (overall survival [OS] and progression free survival [PFS]) vs. placebo and a manageable safety profile (Yoon-Koo Kang, et al. 2017 ASCO Gastrointestinal Cancers Symposium). The combination fluoropyrimidine and platinum is the current standard-of-care (SOC) in the first-line treatment of pts with metastatic G/GEJ cancer that generally achieves a median survival ranging between 11 and 13 months. Therefore, new treatment options are needed to further improve the clinical outcomes of this particular pts population. This multinational, randomized, Phase 2/3 trial will evaluate the efficacy and safety of Nivo plus chemotherapy (S-1 + oxaliplatin [SOX] or capecitabine + oxaliplatin [CapeOX]) as first-line therapy for pts with unresectable advanced or recurrent G/GEJ cancer (ATTRACTION-04; NCT02746796).

Trial design: This trial consists of two parts. The part 1 is a randomized, open-label study to assess the feasibility of Nivo in combination with the first-line chemotherapy, either SOX or CapeOX. In part 2, approximately 650 chemo-naïve pts aged ≥ 20 years with ECOG PS 0-1, and HER2 negative unresectable or recurrent G/GEJ cancer will be randomized to receive chemotherapy (SOX or CapeOX, investigator's choice) plus either Nivo or Placebo. Randomization will be stratified by intensity of PD-L1 expression, ECOG PS score, disease status and geographical region. Primary endpoints are PFS assessed by independent radiological review committee (IRRC) and OS. Secondary endpoints include objective response rate and disease control rate assessed by IRRC and the site investigator, and duration of response and time to response assessed by IRRC. The part 2 study was started in February 2017.

Clinical trial identification: NCT02746796

Legal entity responsible for the study: ONO Pharmaceutical Co., Ltd

Funding: ONO Pharmaceutical Co., Ltd Bristol-Myers Squibb

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778TiP ATTRACTION-05 (ONO-4538-38/BMS CA209844): a randomized, multicenter, double-blind, placebo- controlled Phase 3 study of Nivolumab (Nivo) in combination with adjuvant chemotherapy in pStage III gastric and esophagogastric junction (G/EGJ) cancer

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Background: Nivo, a fully human IgG4 programmed death 1 (PD-1) immune checkpoint inhibitor antibody, has demonstrated survival benefits across various tumor types. In ATTRACTION-02 (ONO-4538-12), a double-blind, placebo-controlled Phase 3 study in patients (pts) with unresectable advanced or recurrent G/EGJ cancer refractory to or intolerant of standard therapy, Nivo alone (3 mg/kg Q2W) achieved significant survival benefits (overall survival [OS] and progression free survival) vs. placebo with a manageable safety profile (Yoon-Koo Kang, et al. 2017 ASCO GI Cancers Symposium). In pStage II/III G/EGJ cancer, postoperative adjuvant chemotherapy with tegafur-gimeracil-oteracil potassium (S-1) or oxaliplatin/capecitabine (CapeOX) is indicated standard of care in Asian countries. However, the efficacy of these treatments is still unsatisfactory in pts with pStage III G/EGJ cancer, and thus a new treatment strategy is required. This multinational trial will evaluate the efficacy and safety of Nivo in combination with standard adjuvant chemotherapy in pts with pStage III G/EGJ cancer (ClinicalTrials.gov Identifier: NCT03006705).

Trial design: In this study, approximately 700 pts between 20 to 80 years of age with pStage III G/EGJ cancer after D2 or more extended lymph node dissection will be randomized to receive adjuvant chemotherapy (S-1 or CapeOX by investigator's choice) + either Nivo or placebo. Treatment with Nivo, placebo, and S-1 therapy will be continued for up to 1 year, and CapeOX therapy will be administered for up to 6 months. Pts will be followed up for 5 years at maximum until consent withdrawal or the start of post-study treatment due to disease relapse. Primary endpoint is relapse free survival (RFS) by central assessment. Secondary endpoints are RFS by site investigator assessments, 3- and 5-year RFS rates by central and site investigator assessments, OS and 3- and 5-year OS rates. Japan, Korea, Taiwan and China will participate into the trial. This study has already started patient enrollment.

Clinical trial identification: NCT03006705

Legal entity responsible for the study: Ono Pharmaceutical Co., Ltd

Funding: Ono Pharmaceutical Co., Ltd, Bristol-Myers Squibb

Disclosure: M. Terashima: Taiho, Chugai, Lilly Japan, Yakult, Daiichi-Sankyo. H.C. Chung: Lilly, GSK, MSD, Merck-Serono, BMS/Ono, Taiho, Celltrion, Quintiles, BMS. N. Boku: Ono, Taiho, Chugai, Eli-Lily. Y-K. Kang: Ono, Bristol-Myers Squibb, Lilly/ImClone, Taiho Pharmaceutical, Roche/Genentech, Novartis, Bayer. L-T. Chen: Ono Pharmaceutical Co., Ltd, Eli Lilly, MSD, PharmaEngine, Merrimack, TTY, Syncore, Five Prime, Novartis, GSK, Merck Serono, Polaris, anti-alpha enolase (ENO-1) monoclonal antibody/HuniLife. M. Sasako: Taiho, Chugai, Lilly, Yakult, Olympus, Daiichisankyo. All other authors have declared no conflicts of interest.

779TiP Adjuvant oxaliplatin plus S-1 (SOX) with concurrent radiotherapy versus SOX alone for gastric cancer with D2 lymph node dissection and high risk factors: a randomized phase III trial

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Background: The role of adjuvant radiotherapy in patients with radical ressected gastric cancer with D2 lymph node dissection is controversial. Patients with high risk factors including late T stage (T4) and positive lymph nodes (N+) were likely to be benefit from adjuvant concurrent chemoradiotherapy. This trial was designed to compare adjuvant chemoradiotherapy, oxaliplatin plus S-1(SOX) and concurrent radiotherapy, with SOX alone in gastric cancer patients with D2 lymph node dissection and high risk factors.

Trial design: This study is a multiple center randomized phased III controlled trial undertaken by The Western Cooperative Gastrointestinal Oncology Group of China (WCGOG). Patients underwent R0 and D2 gastrectomy and pathologic diagnosed $\geq$ T4a or positive lymph node (N+) disease per AJCC 7th edition were enrolled in this study. Eligible patients were randomly assigned to receive adjuvant chemotherapy of SOX regimen and concurrent 3D-CRT/IMRT (50.4Gy/28f) or six cycles of SOX alone. Block randomization was done and stratified by disease stage. Primary endpoints are disease-free survival (DFS). Secondary endpoints are overall survival (OS), local control rate (LCR) and toxicity.

Clinical trial identification: ChiCTR-TRC-12002919

Legal entity responsible for the study: N/A

Funding: None

Disclosure: All authors have declared no conflicts of interest.

780TiP Impact of early palliative care on overall survival of patients with metastatic upper gastrointestinal cancers treated with first-line chemotherapy: Phase III EPIC trial

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Background: Palliative care (PC) has usually been offered at end-life stage, although the World Health Organization recommends providing PC as early as possible in the course of malignancies. Temel et al. (N Engl J Med 2010) have shown that early PC (EPC) provides a favorable effect on quality of life, as well as a surprising benefit on overall survival (OS) (secondary endpoint of this trial) over standard treatment to patients (pts) with metastatic lung cancer. Median OS of pts with metastatic upper gastrointestinal (upGI) cancers does not exceed 10-11 months, which is as poor as that reported with metastatic lung cancers. Whether or not OS benefit with EPC also applies to pts with metastatic upGI cancers is unknown. Demonstration of such benefit in these pts would lead to an earlier integration of PC in oncologic care.

Trial design: EPIC is a randomized phase III trial. It is aimed to estimate the OS benefit of EPC combined with standard oncologic care over standard oncology care only, in pts with metastatic upGI cancers who start 1st-line chemotherapy. Eligibility criteria also include ECOG PS $\leq$ 2, and life expectancy $>$ 4 weeks. Main exclusion criteria include: locally advanced tumors, esogastric cancers with unknown or positive HER2 status, dysphagia, and jaundice. Treatments will be randomized in a 1:1 ratio; a minimization procedure will be used to balance pts according to center, PS (0-1 *vs* 2) and tumor location (esogastric/gastric, pancreas, and biliary tract). Pts will be recruited nationwide, in 17 university hospitals or cancer centers. OS will be used as a primary endpoint. The content of PC visits will be studied through a specific checklist. Patient-reported outcomes (quality of life, depression and anxiety) will be also investigated. Assuming an exponential distribution of survival time, 381 deaths are required to ensure an 80%-power for an absolute difference of 10% in one-year OS (40% vs 50.3%, HR = 0.75; logrank test two-sided alpha=5%), leading to a planned sample size of 480 pts enrolled over 3 years. The main analysis will be performed on the intention-to-treat dataset. Enrollment began on September 2016.

Clinical trial identification: NCT02853474

Legal entity responsible for the study: Centre Oscar Lambret

Funding: None

Disclosure: All authors have declared no conflicts of interest.

781TiP Apatinib and irinotecan combination treatment in first-line chemotherapy refractory esophageal squamous cell carcinoma: A phase I dose escalation study

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Background: Esophageal cancer is one of the common malignant tumors. Different from that in western countries, esophageal squamous cell carcinoma (ESCC) is still the dominant pathological type in China and account for more than 95% of cases in clinic. The annual incidence of esophageal squamous cell carcinoma is 260,000 with the mortality of 210,000 in China. For patients with recurrent or metastatic disease, chemotherapy is one of important treatment alone or with radiotherapy. Taxane, platinum, and fluoropyimidine have been reported effective in ESCC and are popularly used in first-line treatment of ESCC. However, there is still no standard 2nd-line treatment for ESCC patients. Apatinib, also known as YN968D1, is an oral tyrosine kinase inhibitor to vascular endothelial growth factor (VEGFR) receptor, by which blocks the VEGF signaling pathway and results in anti-angiogenesis of tumors. Preclinical data has shown that it is effective in the treatment of a variety of solid tumors including esophageal cancer. And it was approved and launched in China in 2015 as a 3rd-line treatment for patients with advanced gastric cancer. However, the role of anti-angiogenses targeting treatment including apatinib is unknown. Here, we initialize a dose escalation phase I study to identify the dosage of apatinib when combined with irinotecan to treat ESCC patients who were with recurrent disease after esophagectomy and refractory to 1st-line chemotherapy.

Trial design: Patients, age 18-70, with measurable tumor lesion, failed in or progression after 1st line chemotherapy, were enrolled in this 3 + 3 design study. Apatinib dosage escalated from 250 mg, 500mg, to 750mg daily in 3 different cohorts while the dosage of irinotecan was maintained 150mg/m^2 very 2 weeks for 3 cycles (6 weeks). The dose-limiting toxicity (DLT) was identified as grade 4 hematologic toxicity and grade 3 to 4 non-hematologic toxicity according to NCI CTC AE 4.0 criteria. The primary endpoint is the maximum toxic dosage (MTD) and the secondary end points include the objective response rate (ORR), progression-free survival (PFS) and overall survival (OS).

Clinical trial identification: NCT02645864

Legal entity responsible for the study: Dr. Xiaodong Zhang

Funding: HengRui Cancer Research Foundation of CSCO (Y-HR2015-030)

Disclosure: All authors have declared no conflicts of interest.

782TiP PANOVA-3: A phase 3 study of TTFields with gemcitabine and nab-paclitaxel for front-line treatment of locally-advanced pancreatic adenocarcinoma (LAPC)

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Background: TTFields are a non-invasive, regional antimitotic treatment modality, which has been approved for the treatment of glioblastoma by the FDA. TTFields predominantly act by disrupting the formation of the mitotic spindle during metaphase. TTFields were effective in multiple preclinical models of pancreatic cancer. PANOVA was the first trial testing TTFields in pancreatic cancer patients, demonstrating their safety when combined with gemcitabine and nab-paclitaxel, and preliminary promising efficacy in LAPC. PANOVA-3 is designed to test the efficacy of adding TTFields to the same chemotherapy combination in this disease stage.

Trial design: Approximately 600 patients with unresectable, LAPC (per NCCN guidelines) will be enrolled in this prospective, randomized trial. Patients should have an ECOG score of 0-2 and no prior progression or treatment. Patients will be stratified based on their performance status and geographical region. Gemcitabine and nab-paclitaxel will be administered at standard dose. The NovoTTF-100L (150kHz) system will be used by experimental arm patients for at least 18 hours/day until local disease progression per RECIST Criteria V1.1. Follow up will be performed q8w, including a CT scan of the chest and abdomen. Following local disease progression, patients will be followed monthly for survival. Overall survival will be the primary endpoint and progression-free survival, objective response rate, rate of resectability, quality of life and toxicity will all be secondary endpoints.

Legal entity responsible for the study: Novocure

Funding: Novocure

Disclosure: O. Farber, U. Weinberg, Z. Bomzon, M. Giladi, E.D. Kirson: Employee of Novocure

1733PD New promising combination therapy of a mitochondrial metabolism inhibitor with mFOLFIRINOX in pancreatic cancer

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Background: Stage IV pancreatic cancer is a lethal disease. Current standard practice is combination chemotherapy such as FOLFIRINOX or Gemcitabine and Abraxane. The glycolic and mitochondrial metabolism are aberrant in pancreatic cancer and translate into chemoresistance. Inhibition of glutamine metabolism can potentially synergize with therapies that increase intracellular reactive oxygen species such as FOLFIRINOX components. CPI- 613 is a novel antimitocondrial developed by Rafael Pharmaceuticals that showed preclinical activity in pancreatic cancer.

Methods: We designed a phase 1 study to evaluate for synergy between CPI -613 and FOLFIRINOX for patients with stage IV pancreatic cancer. Aims: To determine the maximum tolerated dose (MTD) of CPI- 613 when used in combination with modified FOLFIRINOX. To assess the safety of CPI-613 + modified FOLFIRINOX To obtain preliminary data on efficacy of treatment.

Results: Updated Results as of July, 2017 Toxicity: No deaths due to adverse events were reported. The MTD was identified at 500 mg/m^2 and a total of 18 patients were treated at the MTD. The most common grade 3–4 non-hematological adverse events: hyperglycemia, hypokalemia, peripheral sensory neuropathy, diarrhea, and abdominal pain. The most common grade 3–4 hematological adverse events: neutropenia, lymphopenia, anemia and thrombocytopenia Preliminary efficacy: Of the 18 patients treated at MTD– 8 patients are alive and 3 patients are still on treatment. The median PFS is 10.4 months, 95% CI (119 to 560 days) – 3 patients are still alive and on treatment who have not progressed. Median overall survival is 20.1 months, data still maturing. The 95% CI cannot be accurately estimated yet. Three patients achieved a complete response.

Conclusions: CPI-613 is a first in class non-redox active lipoate derivative being tested in phase I clinical trial in combination with FOLFIRINOX. The MTD for CPI-613 was identified at 500mg/m^2. The treatment combination is feasible and well-tolerated. The response rate was 61%, which is higher than FOLFIRINOX alone (31.6%). The median PFS is 10.4months and the median OS is 20.1 months, data still maturing. A randomized, international phase 3 study of FOLFIRINOX vs. m FOLFIRINOX+ CPI613 will open in 2018.

Clinical trial identification: NCT01835041, First received: April 16, 2013 Last updated: May 30, 2017 Last verified: May 2017

Legal entity responsible for the study: Wake Forest University, School of Medicine

Funding: Cornerstone Pharmaceutical now Rafael Pharmaceuticals

Disclosure: T. Pardee: Chief Medical Officer and employee of Rafael Pharmaceutical (name change on June 5th 2017 from Cornerstone Pharmaceutical). Dr Pardee has no stock or equity in the company. S. Luther: Employee of Rafael Pharmaceuticals and the COO of the company. He owns stock in the company. All other authors have declared no conflicts of interest.

1734PD Anti-CTGF human recombinant monoclonal antibody pamrevlumab increases resectability and resection rate when combined with gemcitabine/Nab-paclitaxel in the treatment of locally advanced pancreatic cancer patients

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Background: Pancreatic ductal adenocarcinomas (PDAC) exhibit a high degree of desmoplasia, with extensive connective tissue growth factor (CTGF) expression and extracellular matrix production[1, 2]. Pamrevlumab (FG-3019), anti-CTGF antibody, is evaluated in fibrotic disease and cancer. Studies in the LSL-Kras$^{G12D/+}$; LSL-Trp53$^{R172H/+}$; Pdx-1-Cre (KPC) transgenic mouse model of PDAC demonstrated that pamrevlumab, in combination with gemcitabine, prolonged survival and increased tumor cell apoptosis associated with the down-regulation of the anti-apoptotic protein XIAP[3].

Methods: In Phase 2 randomized study, gemcitabine/Nab-paclitaxel (G/N) +/- pamrevlumab was given to treatment-naïve locally advanced pancreatic cancer (LAPC) patients to improve resection outcomes and overall survival (OS). 33 LAPC patients were randomized 2:1 to G/N with (Arm A) (n = 22) or without (Arm B) (n = 11) pamrevlumab. Patients who completed 6 cycles of chemotherapy underwent resectability assessment by NCCN and other (CA 19-9, PET, RECIST) criteria, and, if eligible, resection with no further treatment. Patients who progressed received second-line treatment as per physician choice.

Results: No increases in SAEs or surgical complications were observed in Arm A vs Arm B. No significant difference was seen in RECIST, PET or CA 19-9 between the arms. More patients in Arm B (45%, n = 5) than in Arm A (25%, n = 3) discontinued treatment early, mainly due to progression of disease, SAE or physician choice. Of all of the patients who completed 6 cycles of treatment, 78% of patients in Arm A, and 17% of patients in Arm B were deemed resectable; and 44% in Arm A vs 17% in Arm B underwent resection. The primary reasons in patients, who scored as eligible but resected were: metastatic disease, SAE, and physician decision. An improved resection rate was associated with a trend towards improved OS in Arm A.

Conclusions: Improved resection rate combined with increased median OS in Arm A suggests that pamrevlumab is a valuable addition to neoadjuvant therapy in LAPC patients without added toxicity, and that this combination therapy may have a positive impact on OS in LAPC patients.

Clinical trial identification: NCT01890265

Legal entity responsible for the study: Fibrogen Inc.

Funding: Fibrogen Inc.

Disclosure: E. Carrier: Consultant to Targazyme Full time employee of Fibrogen. V. Picozzi: Research funding from Celgene. K. Mody: Research Support: Ipsen, Senwha, Medimmune, Tracon. J. Winter: Research grant from American Cancer Society. J. Glaspy: Consultant for Fibrogen. Research grant from Fibrogen. K. Lipson, S. Porter, E. Kouchakji: Full time employee of Fibrogen. All other authors have declared no conflicts of interest.

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GENITOURINARY TUMOURS, PROSTATE

783O Benefits of Abiraterone Acetate Plus Prednisone (AA+P) When Added to Androgen Deprivation Therapy (ADT) in LATITUDE on Patient (Pt) Reported Outcomes (PRO)

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Background: In the LATITUDE study, treatment with ADT+AA+P significantly improved overall survival and delayed disease progression in pts with newly diagnosed, high-risk, metastatic castration-naïve prostate cancer (mCNPC). In this analysis we evaluated the impact of ADT+AA+P on PROs, including symptom and health-related quality of life (HRQoL) measures.

Methods: 1199 mCNPC pts were randomized 1:1 to ADT + AA+P or ADT + placebos (PBOs). Brief Pain Inventory-Short Form (BPI-SF), Brief Fatigue Inventory (BFI), Functional Assessment of Cancer Therapy-Prostate (FACT-P), and EQ-5D-5L questionnaires were administered at baseline (BL), Day 1 of Cycles (C) 2-13, then every 2 months until treatment discontinuation (TD). EQ-5D-5L were performed every 4 months until 12 months after TD. Time to event and repeated measures analyses on changes from baseline were conducted.

Results: Questionnaire compliance rate was high at ≥ 90%. Compared to ADT+PBOs, the ADT+AA+P arm had significant delayed time to pain and fatigue intensity and interference progression (Table). FACT-P assessments demonstrated significant delay in degradation for the total score and symptom subscales for the ADT+AA+P arm (Table). Repeated measures analyses showed maintenance or improvement from BL for the ADT+AA+P arm compared to the ADT+PBOs arm, with significant differences emerging as early as C2. Significant improvement from BL in EQ-5D VAS for general health status and health utility scores occurred as early as C5 and was maintained throughout the study.

Conclusions: Compared with ADT+PBOs, treatment with ADT+AA+P consistently demonstrated improvement across multiple PRO measures, with statistically significant improvement in HRQoL and delays in progression of pain fatigue intensity and interference, and functional decline. Results for PROs were consistent with improvements in clinical outcomes.

Clinical trial identification: EudraCT: 2012-002940-26 NCT01715285

Legal entity responsible for the study: Janssen Research & Development

Funding: Janssen Research & Development

Disclosure: K. Chi: Consulting/Advisory Role: Janssen Research Funding: Janssen A. Protheroe: Consulting/Advisory Role: IPSEN, Bayer, Roche, BMS Research Funding: Merck Travel, Accommodations, Expenses: BMS A. Rodriguez Antolin: Consulting/Advisory Role: Astellas, Janssen, Bayer Speaker's Bureau: Astellas, Janssen Travel, Accommodations, Expenses: Astellas, IPSEN Pharma H. Suttmann: Honoraria, Consulting/Advisory Role, Research Funding: Astellas, Bayer Health Care, Bristol-Myers-Squibb, Ipsen, Janssen-Cilag, Medac, Santorin-Aventis N. Matsubara: Consulting/Adisory Role: MSD, AstraZeneca, Eisai, Ono, Kissei, Sanofi, Taiho, Takeda, Chugai, Novartis, Bayer, Yakuhin, Pfizer Japan, Merck, Serono, Janssen - Research Funding: Shionogi, Bayer, Yakuhin, Janssen, Chugai, Eli Lilly Japan, Eisai, MSD Z-Q. Ye: Consulting/Adisory Role: MSD, AstraZeneca, Eisai, Ono, Kissei, Sanofi, Taiho, Takeda, Chugai, Novartis, Bayer, Yakuhin, Pfizer Japan, Merck, Serono, Janssen - Research Funding: Shionogi, Bayer, Yakuhin, Janssen, Chugai, Eli Lilly Japan, Eisai, MSD T. Li, P. De Porre, J. Martin: Employment at Janssen Research and Development Stock Ownership of Johnson & Johnson K. McQuarrie, B. Jia, M.B. Todd: Employment at Janssen Research and Development Stock Ownership of Johnson & Johnson K. Fizazi: Honoraria, Consulting/Advisory Role: Astellas, Bayer, Clovis, Curevac, Genentech, Janssen, Orion, Sanofi All other authors have declared no conflicts of interest.

784O Docetaxel (D) with androgen suppression (AS) for high-risk localized prostate cancer (HrPC) patients (pts) who relapsed PSA after radical prostatectomy (RP) and/or radiotherapy (RT): A randomized phase III trial

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Background: HrPC pts with PSA relapse after local therapy may have a poor prognosis and AS may be a therapeutic option. D+AS is standard of care in hormone-naive metastatic PC. We evaluated the benefit of D+AS in HrPC pts with PSA relapse after RP and/or RT.

Methods: Multicenter, randomized phase 3 study (NCT00764166) comparing AS (triptorelin, every 3 months for 1 year) versus AS+D (70 mg/m^2 Q3W, 6 cycles). To be enrolled, pts needed ≥ 3 rising PSA values >0.2ng/mL (after RP) or > 1ng/mL above

Table 783O Time to Progression and Relative Risk for HRQoL End Points

Measure	ADT+AA+P (months)	ADT+PBOs (months)	HR (95% CI)	p Value
Median time to worst pain intensity progression (BPI-SF)	NR	16.6	0.695 (0.583-0.829)	<0.001
Median time to pain interference progression (BPI-SF)	NR	18.4	0.671 (0.561-0.803)	<0.001
Median time to fatigue intensity progression (BFI)	NR	NR	0.652 (0.527-0.805)	<0.001
Median time to fatigue interference progression (BFI)	NR	NR	0.594 (0.470-0.750)	<0.001
Median time to FACT-P degradation				
Total Score	12.9	8.3	0.853 (0.736-0.989)	0.032
Pain-related Subscale	10.2	6.5	0.760 (0.659-0.876)	<0.001
Prostate Cancer Subscale	8.3	5.6	0.808 (0.701-0.930)	0.003

HR, hazard ratio; CI, confidence interval.

Table: 7840

	AS + D (n = 125)	AS alone (n = 125)	HR (95%)	p-value
PSA-PFS (months)	20.7 [19.2-21.5]	18.6 [17.6-20.2]	0.85 (0.62-1.16)	0.31
rPFS (years)	8.8 [7.7-10.2]	9.7 [6.9-10.9]	1.01 (0.72-1.40)	0.95
25eme percentile (OS, years)	8.3	8.1	1.16 (0.76-1.77)	0.49

nadir (after RT) modified by nadir + 2ng/ml (RTOG-ASTRO Phoenix, 2006) and ≥ 1 of the following criteria: Gleason ≥8, PSA doubling time (PSADT) ≤6 mths, PSA velocity >0.75 ng/mL/year, positive surgical margins (SM), pN1, time from curative therapy to PSA relapse ≤12 months. Pts were stratified on type of local treatment (RP or RT) and PSADT (≤ or > 6 mths). Primary endpoint was PSA-PFS defined by a PSA above 0.2ng/ml and rise ≥ 50% from baseline confirmed by 2 subsequent values. Secondary endpoints were PSA response (decrease ≥50%), radiological progression (rPFS), overall survival (OS) and safety.

Results: between 2003-2007, 250 pts (median age 65 years), were randomized to AS+D (arm A, n = 125) or AS (arm B, n = 125). Local treatment: RP (95 pts, 38%), RT (69 pts, 28%) or RP+RT (86 pts, 34%). Risk factors were as follows: Gleason ≥8: 29%, PSADT≤ 6 mths 54%, PSA velocity >0.75 ng/mL/yr 84%, positive SM 37%, pN1 4%, PSA relapse ≤12 mths 45%. 58% of pts had ≥3 risk factors. Six pts had a PSA >20 ng/ml at baseline. There was no significant difference in PSA response (94% vs 98%), PSA-PFS and rPFS between 2 arms (table). Median OS was not mature. Most common grade ≥3 toxicities in arm A were neutropenia (58%), febrile neutropenia (8%) and hair loss (4%). AS toxicities were mainly grade 2 hot flushes (47%) and depression (11%).

Conclusions: AS+D failed to improve PSA-PFS, rPFS in HrPC pts relapsing PSA after local therapy.

Clinical trial identification: NCT00764166

Legal entity responsible for the study: Stéphane OUDARD, MD, PhD

Funding: Sanofi Aventis

Disclosure: S. Oudard: Honoraria from Sanofi, Novartis, Roche, Ipsen, BMS outside submited work L. Miglianico, E. Sevin, A-C. Hardy Bessard: Fees from Sanofi. C. Chevreau, C. Linassier, S. Culine: Fees from Sanofi, Astellas, Janssen. F. Priou: Fees from Sanofi. P. Beuzeboc: Fees from Sanofis, Astellas, Janssen. G. Gravis: Travel paid by Sanofi, Astellas, Janssen All other authors have declared no conflicts of interest.

785O Lutetium-177 PSMA (LuPSMA) theranostics phase II trial: Efficacy, safety and QoL in patients with castrate-resistant prostate cancer treated with LuPSMA

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Background: Progressive metastatic castrate-resistant prostate carcinoma (mCRPC) is a highly lethal condition. Lutetium-177 (^{177}Lu)-PSMA617, a radiolabelled small molecule, binds with high affinity to prostate specific membrane antigen (PSMA) enabling beta particle therapy targeted to mCRPC.

Methods: In this phase II prospective trial, 30 pts with PSMA-avid mCRPC who had failed standard therapies received up to 4 cycles of ^{177}Lu-PSMA617 every 6 weeks. The primary endpoints were PSA and imaging response (PCWG2) and toxicity (CTCAE v4). Other endpoints were quality of life (EORTC QLQ-C30/BM22, BPI), dosimetry, PFS and OS.

Results: All patients were enrolled between 10/2015 and 12/2016 (median age 69 yr, ECOG 1; PSA doubling time 2.2 months) with 3 pts awaiting a final treatment cycle. 87% received prior chemotherapy, 47% cabazitaxel and 83% prior abiraterone and/or enzalutamide. Mean dose was 7.5 GBq (range 4.4 – 8.7 GBq) prospectively adjusted according tumour burden, renal function and weight. At this interim analysis, 17/30 pt (57%) achieved PSA decline >50%, including 11/30 (37%) with decline >80%. In 17 pt with soft tissue disease, objective response (RECIST PR+CR) occurred in 12 pt (71%). Most common adverse events were grade 1 xerostomia (19 pt, 63%) and nausea (15 pt, 50%). Grade 3 or higher hematoxicity occurred in 5 pt (17%); all had baseline thrombocytopenia and were reversible. Following the first cycle of LuPSMA, global health score improved significantly (≥10 points) in 11/30 pt (37%), while in those with bone pain, mean severity score improved significantly (≥ 10 points) in 9/21 pt (43%).

Conclusions: The LuPSMA Phase II trial provides evidence of high response rates and low toxicity with improved QoL and pain reduction in men with mCRPC who have failed conventional therapies.

Clinical trial identification: Australian New Zealand Clinical Trials Registry: ACTRN12615000912583. Universal Trial Number (UTN): U1111-1172-4095.

Legal entity responsible for the study: Peter MacCallum Cancer Centre, Melbourne, Australia

Funding: Investigator-initiated trial. Lutetium-177 (no carrier added) supplied by Australian National Nuclear Research and Development Organisation (ANSTO). PSMA617 supplied by Advanced Biochemical Compounds (ABX).

Disclosure: All authors have declared no conflicts of interest.

786PD DNA repair gene panel mutations in young onset and aggressive vs non aggressive prostate cancer cases in the UK

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Background: Prostate cancer (PrCa) is the most common solid tumour in men in the Western world. There is evidence that PrCa predisposition is due to germline common and rare variation.

Methods: We sequenced 175 genes in the DNA damage response and repair pathways using an Agilent custom capture kit and Illumina technology in PrCa cases diagnosed at < 65 years compared with controls in the UK (mean coverage 76X). Data were analysed from 1346 PrCa cases and 1186 controls using a GATK 2.8 analysis pipeline.

Results: We identified 5,118 single nucleotide variants (SNVs) and 172 indels; 216 unique protein truncating variants (PTVs) were in 96 genes of the 175 gene panel. The total number of PTVs in cases was significantly higher (181) than in controls (122); in particular, in the BROCA gene set of 22 tumour suppressor genes (P = 0.002). Mutations in *BRCA1, BRCA2, ATM, MSH5* and *CHEK2* were 3 times more common in cases compared with controls (P = 0.0018). To investigate if aggressive cases had a different mutation burden we compared 204 aggressive (Gleason score>8) versus 1049 non-aggressive (Gleason score ≤7) cases. In the single variant analysis, one variant in *BRCA2*, rs28897754 (K2950N) showed association with a more aggressive phenotype (P = 0.0016). Gene burden testing showed *BRCA2, MSH2, PALB2* and *CHEK2* had an OR > 3 in aggressive v non aggressive cases (14% v 4% respectively). Men who died of PrCa had a 17% incidence of mutation in a subset of the 175 gene panel.

Conclusions: We have shown that there is a higher percentage of DNA damage response and repair gene germline mutations in PrCa cases occurring at < 65 years, in those with aggressive and lethal disease and this result will enable us to develop a testing panel for use in clinical care in the near future.

Clinical trial identification: UKGPCS - CCR0848 & 06/MRE02/4

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

Funding: None

Disclosure: All authors have declared no conflicts of interest.

787PD Prognostic associations of prostate-specific antigen (PSA) decline with survival, radiographic response and progression in chemotherapy-naïve men with metastatic castration-resistant prostate cancer (mCRPC) treated with enzalutamide

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Background: In the PREVAIL clinical trial, enzalutamide provided significant improvements vs placebo in radiographic progression-free survival (rPFS) and overall survival (OS) in chemotherapy-naïve men with mCRPC. This post hoc analysis aimed to evaluate the prognostic association between the magnitude of PSA decline from baseline and clinical outcomes in PREVAIL.

Methods: Men from the enzalutamide and placebo arms of PREVAIL were grouped into categories of confirmed maximal PSA decline from baseline at month 3 of

Table: 787PD

Outcome	Maximal PSA Decline From Baseline at Month 3 in the Enzalutamide Arm (N = 872)			
	No Decline/ Decline < 30% (n = 94/872)	≥ 30% Decline (n = 701/872)	≥ 50% Decline (n = 639/872)	≥ 90% Decline (n = 307/872)
Best objective soft-tissue response (CR or PR), % (95% CI)	12.0 (4.5-24.3)	70.6 (65.1-75.6)	74.8 (69.2-79.9)	89.7 (82.8-95.0)
Median (95% CI) time to PSA progression, mo	3.7 (3.7-4.6)	13.8 (11.3-14.0)	13.9 (13.8-16.6)	22.5 (16.8-NYR)
Median (95% CI) rPFS, mo	7.9 (3.7-NYR)	NYR (13.8-NYR)	NYR (13.8-NYR)	NYR (13.8-NYR)
HR (95% CI) for rPFS	1.0 (ref)	0.20 (0.13-0.31)	0.17 (0.11-0.27)	0.10 (0.05-0.19)
Median (95% CI) OS, mo	23.1 (17.8-28.0)	32.4 (31.5-NYR)	NYR (31.5-NYR)	NYR (NYR-NYR)
HR (95% CI) for OS	1.0 (ref)	0.31 (0.22-0.42)	0.28 (0.20-0.39)	0.19 (0.12-0.28)

Abbreviations: CI, confidence interval; CR, complete response; HR, hazard ratio; mo, months; NYR, not yet reached; OS, overall survival; PR, partial response; PSA, prostate-specific antigen; ref, reference, rPFS, radiographic progression-free survival.

treatment: no decline/decline < 30% and ≥ 30%, ≥ 50% or ≥ 90% decline. Confirmation required PSA decline on ≥ 1 consecutive visit after month 3. Best overall soft-tissue response (per RECIST v1.1) was determined for patients with measurable disease at baseline (data cutoff: 16 Sep 2013). Time to PSA progression (data cutoff: 16 Sep 2013), rPFS (per PCWG2; data cutoff: 6 May 2012) and OS (data cutoff: 16 Sep 2013) were estimated using the Kaplan-Meier method.

Results: In PREVAIL, men were randomized to enzalutamide (n = 872) or placebo (n = 845). Most men in the placebo arm (66%, 558/845) had no PSA decline/decline < 30%, in contrast to 11% (94/872) in the enzalutamide arm. In the enzalutamide arm, 81% (701/872) of men had a PSA decline of ≥ 30% from baseline at week 13, 73% (639/872) had a PSA decline of ≥ 50% and 35% (307/872) had a PSA decline of ≥ 90%. Key outcomes for the enzalutamide arm are provided by PSA decline category in the Table. PSA flare (rise followed by a fall) after 3 months was rare with enzalutamide (< 1%).

Conclusions: PSA declines after 3 months of enzalutamide therapy are strongly associated with soft-tissue response and improvements in rPFS and OS. Providing updated prognostic information to chemotherapy-naïve men with mCRPC can be of clinical value given the heterogeneity of long-term outcomes.

Clinical trial identification: NCT01212991

Legal entity responsible for the study: This study was sponsored by Medivation, Inc. (which was was acquired by Pfizer, Inc. in September 2016) and Astellas Pharma, Inc., the co-developers of enzalutamide.

Funding: This study was sponsored by Medivation, Inc., (which was acquired by Pfizer, Inc. in September 2016) and Astellas Pharma, Inc., the co-developers of enzalutamide.

Disclosure: A.J. Armstrong: Consultant: Bayer, Sanofi, Novartis, Dendreon, Medivation, Janssen Biotech, Eisai Bureau: Dendreon, Sanofi, Medivation, Janssen Biotech Grant/Patent (inst) Dendron, Sanofi, Bayer, Pfizer, Novartis, BMS, Janssen Oncology, Medivation, Astellas, Gilead. P. Lin, T. Parli: Employment: Pfizer, Inc. C.S. Higano: Consulting/Travel: Dendreon, Bayer, Medivation, Ferring, J&J, AbbVie, Genentech, Pfizer, BHR, Orion, Sanofi, Amgen, Ockham, Teva, Astellas. P. Iversen: Consultant/Advisor, Meeting Participant/Lecturer, Scientific Study/Trial and Clinical Research Collaboration: Astellas Pharma, Medivation. C.N. Sternberg: Honoraria: Pfizer, Bristol-Myers Squibb, Novartis, Janssen, Bayer, Astellas Pharma, Sanofi, Eisai, Ipsen, GlaxoSmithKline, MSD. B. Tombal: Consulting: Astella, Bayer, Ferring, Janssen, Takeda, Steba Biotech, Sanofi Speakers Bureau: Amgen, Janssen Travel/Honoraria: Amgen, Astellas, Bayer, Ferring, Janssen, Sanofi. D. Phung: Employment: Astellas Pharma. A. Krivoshik: Employment and Travel/Expenses: Astellas Pharma Stock/Ownership Interests: Abbott Laboratories, AbbVie. T.M. Beer: Consulting: Astellas, Bayer, Dendreon, Janssen Japan, Novartis, AstraZeneca, Churchill, Proacta Stock/Ownership: Salarius.

788PD Randomized controlled trial comparing radiotherapy +/- endocrine therapy versus endocrine therapy alone for PSA failure after radical prostatectomy: Japan Clinical Oncology Group Study JCOG0401

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Background: A standard therapy has not been established on PSA failure after radical prostatectomy for localized prostate cancer. Therefore, the randomized controlled trial was designed to confirm the superiority of radiotherapy ± endocrine therapy over endocrine therapy alone for PSA failure after radical prostatectomy.

Methods: Patients were randomly assigned to arm A [endocrine therapy only: bicalutamide (BCL) monotherapy followed by LH-RH agonist in case of BCL failure], or arm B [64.8 Gy of salvage radiotherapy (SRT) followed by same regimen of arm A in case of treatment failure of SRT]. The primary endpoint is time to treatment failure (TTF) of BCL, and secondary endpoints are TTF of protocol treatment, clinical relapse-free survival (RFS), overall survival (OS), adverse events. The planned sample size was 210 to detect improvement of median TTF of BCL from 5 years to 8.3 years with one-sided alpha of 5% and power of 80%. This trial is registered with UMIN-CTR (C000000026).

Results: A total of 210 patients (105 patients in each arm) were registered from May 2004 to May 2011. The TTF of BCL was significantly better in arm B as shown in Table 1 (Hazard ratio 0.56 90% CI (0.40–0.77); one-sided p = 0.001). The 33 patients (32%) of 102 patients with SRT of arm B had no treatment failure of SRT, resulting in being free from hormonal therapy. In addition, TTF of protocol treatment was also significantly better in arm B. However, clinical RFS and OS were similar between the arms. Grade 4 adverse event was reported in one patient in arm B.

Conclusions: The first SRT had advantage in both TTF of BCL and protocol treatment. Although the clinical outcomes of both arms of salvage therapy were similar with each other in terms of clinical PFS and OS, the SRT was effective in 32% of the patients, which contributed to avoiding the salvage endocrine therapy.

Clinical trial identification: UMIN-CTR (C000000026)

Legal entity responsible for the study: Japan Clinical Oncology Group, JCOG

Funding: Ministry of Health, Labor and Welfare of Japan

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Table: 788PD

	Arm A (endocrine therapy only) (95% CI)	Arm B (radiation +/- endocrine therapy) (95% CI)	Hazard Ratio (95% CI)
5-year TTF of BCL	57.0% (46.7%–66.0%)	69.7% (59.6%–77.7%)	0.56 (0.38-0.82)
5-year TTF of protocol treatment	67.0% (56.9%–75.3%)	76.8% (67.1%–83.9%)	0.66 (0.44-1.00)
5-year clinical RFS	93.8% (86.8%–97.2%)	88.9% (80.9%–93.7%)	0.90 (0.45-1.81)
5-year OS	99.0% (93.4%–99.9%)	91.4% (84.2%–95.4%)	1.03 (0.46-2.29)

Peptide Pharmaceutical Co., Ltd. All other authors have declared no conflicts of interest.

789PD Abiraterone acetate (AA) + prednisolone (P) for metastatic castration-resistant prostate cancer (mCRPC) with early progression or non-response to androgen deprivation therapy (ADT)

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Background: mCRPC with early progression (≤1year) or non-response to initial ADT carries a poor prognosis, and there is no consensus regarding second-line therapy for these patients (pts) [ADT poor responders]. Although AA+P is effective for chemo-naïve mCRPC, limited data is available for ADT poor responders; thus, we conducted this study to evaluate the efficacy and safety of AA+P as secondary treatment for this population.

Methods: This was a multicenter, open-label, single arm, 2-stage trial according to Simon's minimax design [hypothesis: p_0=0.150, p_1=0.350, $\alpha = 0.025$, $\beta = 0.100$], and 48 pts were required to efficacy analysis. Key eligibility: Chemo-naïve mCRPC (testosterone level <50 ng/dL under medical/surgical castration), age ≥20, and evidence of prostate specific antigen (PSA) progression by PCWG2 criteria ≤1 year or without achieving a normal PSA level (<4 ng/mL) during initial ADT. For eligible pts, 1000 mg AA with 10 mg P was administered until disease progression. The primary endpoint was the proportion of patients achieving a PSA decline of ≥ 50% from baseline after 12 weeks of treatment in accordance with PCWG2 criteria (PSA response rate).

Results: Fifty pts were enrolled and 49 were evaluable for efficacy analysis. At baseline, the median age was 73 (range 55–86), the median PSA level was 28.34ng/mL (2.28-294.25), and the median duration of initial ADT was 6.4 months (1.4 –18.8). Among the patients, 90.0% had a total Gleason score ≥8, and all had a treatment history of bicalutamide. Most patients showed high treatment compliance (>95% with AA [n = 47/50, 94.0%] and P [n = 46/50, 92.0%]). PSA response rate was 55.1% (n = 27/49; 95%CI 41.3-68.1), and the PSA decline began after 4 or 8 weeks from baseline. The treatment was well tolerated with <25% of grade ≥3 adverse events.

Conclusions: This is the first study to investigate the efficacy of AA+P for ADT poor responders. The study demonstrated similar efficacy to the Phase 3 study COU-AA-302, which further supports the efficacy of AA+P for ADT poor responders. AA + P appears to be a promising treatment for initial ADT poor responders with an acceptable safety profile. This study is ongoing as follow up on time to PSA progression.

Clinical trial identification: NCT02405858 (March 27, 2015).

Legal entity responsible for the study: Janssen Pharmaceutical K.K.

Funding: Janssen Pharmaceutical K.K.

Disclosure: G. Arai: Clinical trials sponsored by AstraZeneca, Green Peptide, Janssen, MSD and Shionogi during the conduct of the study. M. Ogi, T. Takahara, K. Fukushima, K. Yoshizawa: Eemployee of Janssen Pharmaceutical K.K. K. Kobayashi: Clinical trials sponsored by Astellas, Bayer, Janssen and MSD during the conduct of the study. N. Okuno: Clinical trials sponsored by Astrazeneca, Janssen and Pfizer during the conduct of the study.

790PD Safety and immunogenicity of a DNA-vaccine immunotherapy in men with biochemically (PSA) relapsed prostate cancer

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Background: DNA vaccines INO-5150 (PSA and PSMA) +/- INO-9012 (IL-12) were administered to biochemically recurrent prostate cancer patients (pts) to demonstrate breaking tolerance, assessing antigen-specific humoral and cellular immune responses with the potential for stabilization of disease progression.

Methods: Phase I, open-label, multi-center study in pts post-definitive therapy with a rising PSA after surgery and/or RT and PSA doubling time (DT)> 3 months (mos), testosterone > 150 ng/dL, no concomitant ADT and no evidence of metastases. Safety, immunogenicity and efficacy were evaluated in 4 treatment arms in 60 planned pts (A: 16, 2mg INO-5150; B: 15, 8.5 mg INO-5150; C: 15, 2mg INO-5150 + 1mg INO-9012; D: 16, 8.5mg INO-5150 + 1mg INO-9012) treated with 4 IM doses followed by electroporation on day 0, wks 3, 12 and 24 who were followed for a total of 72 Wks.

Results: Median age, Gleason score and time since diagnosis were 69.5 yrs (range: 55.4-87.7), 7 (5-10) and 8.4 yrs (0.4-23.8) respectively. Of 61 evaluable pts, 38 (62%) had PSADT ≤ 12 mos and 23 (38%) had DT > 12 mos at Day 0. For pts with DT ≤ 12 mos, Day 0 and week 27 median DT were 6.0 (1.5, 11.6) mos and 8.1 (2.2, 100.0) mos respectively. Flow cytometry analysis revealed antigen specific upregulation of CD38 and Perforin on CD8+ T cells in 19/50 (38%) pts across the trial, with the greatest proportion in arm A, 8/14 (57%). Additional analysis for this cell subset showed a high PD-1 expression of 68.6% in this arm at week 27. Of note, in 8/15 (53%) arm A pts with DT ≤ 12 mos, their median DT at Day 0 was 6.2 (2.9, 10.2) mos and 19.2 (6.6, 100.0) mos at Wk 27. Safety: 7 Grade (Gr) 3 SAEs in 5 pts and 0 Gr 4-5 SAEs reported. Most AEs were Gr 1-3 in 51/62 (82%) pts and majority of those were associated with injection site reactions.

Conclusions: INO-5150 +/- INO-9012 was safe at dosages examined. Data demonstrated both PSA and PSMA are immunogenic and INO-5150 induced cellular immune responses. Higher proportion of arm A pts showed immunological responses as well as improvements in PSA DT, specifically pts with DT ≤ 12 mos suggesting correlation of immunological efficacy and clinical benefit. Continued analyses are planned as patient follow-up is ongoing. (NCT02514213)

Clinical trial identification: NCT02514213; July 29, 2015

Legal entity responsible for the study: Inovio Pharmaceuticals

Funding: Inovio Pharmaceuticals

Disclosure: K. Bhatt: Inovio (study sponsor employee), own stocks M. Morrow, T. McMullan, K. Kraynyak, J. Lee, B. Sacchetta, L. Liu, S. Rosencranz: Inovio (study sponsor) employee, own stocks in company. Y. Whang: Research funding from Janssen, Astellas, Tokai, Inovio. I. Csiki, M. Bagarazzi: Employed by Inovio Pharmaceuticals. All other authors have declared no conflicts of interest.

791PD Re-education of tumor-associated macrophages by CXCR2 blockade drives senescence enhancement and tumor inhibition in advanced prostate cancer

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Background: Tumor-associated macrophages (TAMs) represent a major component of the tumor microenvironment that supports tumorigenesis. TAMs re-education instead that eradication has been recently proposed as a strategy to promote tumor inhibition.

Methods: We performed an immunophenotyping of Pten null prostate murine models by flow cytometry and gene expression analysis. Immunoistochemistry and immunofluorescence sainings were utilized to detect macrophages infiltration in the tumor and marker of proliferation and senescence in the tissue.

Results: We have found that aggressive prostate tumors are strongly infiltrated by TAMs that express alternatively activated M2 markers. Unexpectedly chemokines binding to the C-X-C chemokine receptor type 2 (CXCR2) were among the most upregulated factors secreted by *Pten* null tumors and controlled the functional polarization of TAMs toward an "M2-like" functional status. Pharmacological blockade of the CXCR2 receptor in different tumor models in vivo promoted the re-education of TAMs toward a pro-inflammatory phenotype, which resulted in induction of senescence and tumor inhibition. Strikingly, infusions of CXCR2 knockout monocytes in $Pten^{pc-/-}$; $Trp53^{pc-/-}$ mice demonstrated that inhibition of CXCR2 does not interfere with the tumor recruitment of monocytes but prevented the polarization of TAMs in M2-like resulting in an increased percentage of TNFα-releasing M1-like macrophages in the tumor microenvironment. Moreover, tumor cells harboring *PTEN* deletion were more sensitive to TNFα-induced senescence when compared to *PTEN* WT tumors due to increased levels of *TNFR1*.

Conclusions: Taken together our results identify TAMs as a target for prostate cancer therapy and describe new therapeutic strategies to harness the anti-tumorigenic potential of macrophages in cancer.

Legal entity responsible for the study: Institute of Oncology Research

Funding: ERC/Steiner

Disclosure: All authors have declared no conflicts of interest.

792PD Phase I, open-label, dose-finding study of GSK2636771, a phosphoinositide 3-kinase (PI3K)β inhibitor, in combination with enzalutamide in male subjects with metastatic castration-resistant prostate cancer (mCRPC)

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Background: GSK2636771 is a potent, adenosine triphosphate (ATP) competitive, selective, oral inhibitor of the PI3Kβ isoform that inhibits the growth of phosphatase and tensin homolog (PTEN) deficient tumor cells in preclinical models. Resistance to the androgen receptor (AR) inhibitor enzalutamide (Xtandi®) may be mediated through upregulation of the PI3K pathway. Thus, GSK2636771 may enhance PTEN deleted prostate cancer cell kill.

Methods: Within 30-days of documented progression on enzalutamide, subjects with PTEN deficient mCRPC are enrolled and treated with enzalutamide plus GSK2636771 in either dose escalation (DE) or dose expansion (DX) phases. Treatment continues until progressive disease (PD), unacceptable toxicities, consent withdrawal, or death. The primary objective is to assess safety, tolerability and determine the recommended phase 2 dose of this treatment combination. Secondary objectives include evaluation of pharmacokinetics, pharmacodynamics, biomarkers, and clinical activity per PCWG2/RECIST 1.1. All subjects receive 160 mg enzalutamide once daily (QD) + GSK2636771 starting at 300mg QD using a standard 3 + 3 DE design with planned 100 mg incremental escalations or de-escalation.

Results: In this ongoing study, 23 subjects received this treatment combination; 7 at 300 mg, 16 at 200 mg. Most AEs were Grade 1 or 2, with diarrhea the most common treatment-related AE (9/23; [39%]). Dose-limiting toxicities (DLTs) included Grade 3 hypocalcemia and reversible Grade 3 acute renal failure at 300mg and Grade 3 rash at 200mg. PK parameters suggested no drug-drug interaction between enzalutamide and GSK2636771. Among 13 evaluable patients at 200mg, 1 had a radiological partial response, and 2 had maximum PSA reductions of $>50\%$. Five subjects have been treated for $\geq$6 months. DE of 300 mg and DX of 200 mg cohorts are ongoing.

Conclusions: Our preliminary data indicate that GSK2636771 in combination with enzalutamide is largely well tolerated and confirm the clinical relevance of PI3Kb inhibition in PTEN-deficient mCRPC. GSK funds this study.

Clinical trial identification: Protocol Number: 200331; NCT02215096; EudraCT No: 2013-005111-27

Legal entity responsible for the study: GlaxoSmithKline

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793PD Phase 1 study of the PSMA-targeted small-molecule drug conjugate EC1169 in patients with metastatic castrate-resistant prostate cancer (mCRPC)

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Background: Prostate-specific membrane antigen (PSMA) is highly expressed in prostate cancers, but not in most non-prostate normal tissues, making it a potential therapeutic target. EC1169, a PSMA-targeted conjugate of the microtubule inhibitor tubulysin B hydrazide is being studied in a two-part phase 1 dose escalation (A)/expansion (B) study in mCRPC. The utility of the PSMA-targeted companion imaging agent ^{99m}Tc-EC0652 is also being evaluated as a patient selection tool. Part A has been completed. We now report the part B data on pts treated to date.

Methods: EC1169 is administered as an IV bolus on days 1, 8 every 21 days. The RP2 dose of 6.5 mg/m^2 was determined in Part A. Part B pts are treated at the RP2 dose and enrolled in 1 of 2 cohorts: mCRPC taxane naïve (cohort 1, 45 pts) or taxane exposed (cohort 2, 40 pts). Prior to treatment, pts undergo a ^{99m}Tc-EC0652 SPECT/CT scan. The primary endpoint of Part B is median radiographic progression-free survival (rPFS). Other study evaluations are OS, PSA, and CTC-based biomarkers.

Results: Thirty-four of a planned 85 pts in Part B have been treated (14 taxane naïve, 20 taxane exposed). Median age is 70 (range: 49-84). Median number of cycles is 3 (range: 1-7). Twenty-six pts (76.5%) reported at least 1 treatment related AE. Most treatment related AEs (TRAEs) are Gr1 and 2; G3 treatment-related constipation occurred in 1 pt. No Grade 4 TRAEs have been reported. No dose reductions due to AEs have occurred. Six of twelve evaluable taxane-exposed pts in Part B had stable disease or better at their first post-baseline scan (9 wks). One pt currently beyond the 18-week scan has achieved durable resolution of his soft tissue disease. Imaging with ^{99m}Tc-EC0652 suggests excellent disease localization.

Conclusions: The RP2 dose of EC1169 is 6.5 mg/m^2 (D1, 8 every 21 days). EC1169 has been well tolerated in 34 Part B pts at the RP2 dose A PSMA-targeted therapeutic strategy appears viable. There is evidence of anti-tumor activity in both the taxane naïve and taxane exposed pts.

Clinical trial identification: NCT02202447

Legal entity responsible for the study: Endocyte, Inc.

Funding: Endocyte, Inc

Disclosure: A. Armour, M. Groaning: Employee of Endocyte, owns company stock. R. Messmann: Contractor for Endocyte, owns company stock. All other authors have declared no conflicts of interest.

794P EPI-506 (ralaniten acetate), a novel androgen receptor (AR) N-terminal domain (NTD) inhibitor, in men with metastatic castration-resistant prostate cancer (mCRPC): Phase 1 update on safety, tolerability, pharmacokinetics and efficacy

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Background: EPI-506 (ralaniten acetate) is being studied in a Phase 1/2 study as a first-in-class transcription inhibitor of the AR NTD.

Methods: Open-label, single-arm, Phase 1/2 study evaluating EPI-506 administered orally. The Phase 1 is a modified 3 + 3 design to establish safety, tolerability, pharmacokinetics (PK), maximum-tolerated-dose (MTD) and the recommended phase 2 dose (RP2D) of EPI-506. Anti-tumor activity is evaluated by PSA and imaging. Inclusion criteria include: mCRPC with progression after > =1 line of hormonal therapy or chemotherapy, failure to treatment with enzalutamide and/or abiraterone.

Results: Twenty-one patients (pts) have been enrolled in the dose escalation phase over 6 dose levels (80 - 2,400 mg). Median age was 72 (range 58-87). Prior treatments included enzalutamide only (N = 9), abiraterone only (N = 3) or both (N = 9). Eight pts also had prior chemotherapy. Twelve pts discontinued due to disease progression and 2 pts due to adverse events (AEs): Grade 4 elevated amylase (probably related; at 640mg) and Grade 4 gastrointestinal bleeding (unrelated). Median exposure was 87 days at cut-off (range 21-418). Most frequently reported treatment emergent AEs were diarrhea (N = 8), nausea (N = 6), and pain in extremities (N = 5). One possibly related Grade 3 AE (AST elevation) was observed at 1280 mg. PK data demonstrate a dose-proportional profile for C_{max} and AUC together with a positive food effect above 640 mg. Three of 21 evaluable pts demonstrated PSA declines ranging from 4 – 29%, and one pt with unchanged PSA at doses >1,280 mg. Three pts have had prolonged treatment (median of 286 days; range 219 – not reached), after intrapatient dose escalation. The study is currently enrolling pts with a total dose of 3,600 mg in both a QD and a BID dosing schedule.

Conclusions: EPI-506 is well-tolerated with an acceptable safety profile. PK indicates dose-proportionality. PSA declines and stable disease have been observed at higher dose cohorts in this ongoing study. This study is the first to evaluate targeting the AR NTD, a region critical for transcriptional function of all known AR species.

Clinical trial identification: NCT02606123

Legal entity responsible for the study: ESSA Pharmaceuticals

Funding: ESSA Pharmaceuticals

Disclosure: U. Vaishampayan, M.S. Gordon, D.C. Smith: ESSA Pharmaceuticals Corp. (Research funding) R.B. Montgomery, K.N. Chi: ESSA Pharmaceuticals Corp. (Scientific advisory board; Honoraria received; Research funding). K. Barber, F. Perabo, N. Thapar, C. Chandhasin: ESSA Pharmaceuticals Corp. (Employed, Ownership interest). A. de Haas-Amatsaleh: ESSA Pharmaceuticals Corp. (Consultant).

796P Phase I expansion cohort of TAS-115, a novel oral MET/VEGFR/FMS inhibitor, for castration-resistant prostate cancer patients (CRPC pts) with bone metastases

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Background: TAS-115 is a novel small-molecule inhibitor of hepatocyte growth factor receptor (MET) and vascular endothelial growth factor receptor (VEGFR) with antitumor activity in preclinical models. It has also been shown that TAS-115 inhibits Feline McDonough Sarcoma oncogene (FMS) kinase, essential for the differentiation of osteoclasts, and is expected to be effective against bone metastases. In this expansion cohort of phase I trial, the safety and efficacy of TAS-115 were evaluated in CRPC pts with bone metastases.

Methods: Eligible CRPC pts with bone metastases who were refractory to standard treatment including docetaxel, abiraterone and/or enzalutamide were enrolled. Two dose levels of TAS-115 (450 and 650 mg/body/day) were administered orally with a 5-days-on/2-days-off schedule for up to 21 days per cycle in this expansion cohort. Efficacy was evaluated based on the RECIST ver 1.1 and bone scan response, defined as 30% decrease in bone scan index (BSI) calculated by quantitative software of BONENAVI®(FUJIFILM RI Pharma, Japan; EXINI bone®, Exini Diagnostics, Sweden). Toxicities were evaluated based on the CTCAE ver 4.03.

Results: As of Apr 2017, a total of 15 pts received TAS-115 (9 pts with 450 mg, and 6 pts with 650 mg). Bone scan response was reported in 4 of 9 pts (44.4%) who had baseline BSI ≥0.5%, which is equivalent to grade≥1 extent of disease. The best overall response per RECIST was stable disease in 7 of 15 pts (46.7%). These efficacies were observed regardless to dose levels. One patient had a long administration period exceeded to 15 months without disease progression, and another one patient experienced remarkable pain relief induced by bone metastases. TAS-115 had no effect on the PSA and ALP. The major (≥30%) adverse drug reactions (ADRs) were anorexia, fatigue, nausea, thrombocytopenia, rash, AST increased, anemia, vomiting and edema. The rate of grade ≥3 to all ADRs was 18.8%. These AEs were recovering by interruption of TAS-115.

Conclusions: Toxicities of TAS-115 were acceptable and manageable in CRPC pts, and preliminary anti-tumor activity, especially against bone metastases was recognized. A phase II trial for CRPC pts with bone metastases is ongoing.

Clinical trial identification: JapicCTI-132333/163448

Legal entity responsible for the study: Taiho Pharmaceutical CO., LTD.

Funding: Taiho Pharmaceutical CO., LTD.

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797P Phase II trial of SM88 in non-metastatic biochemical recurrent prostate cancer

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Background: Despite toxicity and no clear clinical benefit, non-metastatic recurrent prostate cancer (nmPC) is typically treated with medical castration in North America. SM88 is a non-toxic novel combination therapy based on the Warburg effect, with activity in a variety of cancers including prostate (JCO 2017 e Abstract1). End of phase 1 results demonstrated stable or rising testosterone levels while achieving CTC (circulating tumor cells) benefit and no radiographic progression events (JCO 2017e Abstract2). We now report phase II data.

Methods: Starting in Sept 2016, a prospective Phase Ib/II of SM88 (230mg po bid) enrolled recurrent nmPC with rising PSA (PCWG3 definition) and detectable CTCs, but no radiographically identified lesions.

Results: 8 (of 34 planned) subjects have completed at least 1 cycle (median 5, range 1-7). Mean age was 69.7 (62-80); all had prior ADT after curative intent RT (50%) or surgery (50%); no patient is currently on ADT. Mean testosterone level (T) was 581.4 ng/

dL and rose or remained stable in the subjects except for one patient who entered the trial castrate (<2.5) from prior RT. Overall 62.5% had some grade 1-2 adverse event (AE) but there were no drug related serious AE. EORTC-QOL-P30 relating to intimacy (Q50-54) improved or remained stable. In subjects with more than 1 cycle (n = 5), CTCs fell to undetectable (n = 1) or decreased by >30% (n = 4); at up to 6 cycles, no PSA progression (PCWG3) and no radiographic progression was reported (n = 8). No subject required other toxic therapy (100% subsequent treatment free survival). Available preliminary neutrophile:lymphocyte ratio (N::L)(n = 6) improved while urinary NTx, bone specific AlkPhos and LDH trends were essentially unchanged.

Table: 797P

subject #	cycles completed	T ng/dL	CTCs baseline	Max Decrease	N:L Max Decrease
1	6	635.7	26.75	100%	78%
2	6	<2.5	44.75	77%	37%
3	6	340.7	16.75	39%	35%
4	4	154.7	30.75	84%	29%
5	3	162.5	12.5	32%	8%
6	1	557.8	na	na	13%

Conclusions: We propose that hormonal castration is not necessary for nmPC disease control based on a preliminary assessment of both Phase Ib and II data of SM88. CTCs and N::L were improved while maintaining normal T. These early biomarker indicators are consistent with the observed 100% radiographic progression free survival and avoidance of additional toxic therapy. A phase III RCT is planned for confirmation of these results.

Legal entity responsible for the study: Tyme Inc

Funding: Tyme Inc

Disclosure: G. Del Priore, S. Hoffman, G. Sokol: Current or potential ownership of stock or options and/or salary support from Tyme Inc. W-T. Chen, H. Dong: Employee of Vitatex. Tyme Inc has a commercial relationship with Vitatex whereby Vitatex provides blinded results to the CRO supervising the ongoing clinical trial.

798P Impact of the addition of metformin (Met) to abiraterone (Abi) in metastatic castration-resistant prostate cancer (mCRPC) patients (pts) progressing on Abi treatment: A phase II pilot study

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Background: Abi has become one of the standard 1st line treatments in mCRPC. Cross-talk signalling pathways such as PI3K/Akt/mTOR represent a possible resistance mechanism against Abi. The oral antidiabetic agent Met has been shown to have antiproliferative effects via inhibiting mTOR. We hypothesized that the addition of Met to pts with PSA progression on Abi could influence resistance to Abi and thus delaying start of second line therapy.

Methods: Men with mCRPC experiencing PSA progression on first line Abi were enrolled in this prospective single-arm open-label multicentre Phase II trial. Pts with visceral metastases were excluded. Abi (1000mg qd)/Prednisone (5mg bd) treatment was continued and pts received Met 1000mg bd in addition. Primary endpoint was progression-free survival (PFS) at 12 weeks according to RECIST 1.1 or PCWG2 criteria. Secondary endpoints included PFS, PSA response rate, OS, toxicity and safety. 25 pts were planned to consider the trial uninteresting (H0: PFS at 12 weeks $\leq$ 15%) or promising (H1: $\geq$ 35%) using a 5% significance level and a 80% power.

Results: 25 pts with a median age of 76 years (IQR 72-82), were included between November 2013-September 2016 in 3 Swiss cancer centres. Median time to development of castration resistance was 19.5 months (mts) (IQR 11-24), and median duration on Abi before study entry was 12.1 mts (IQR 8-19). PFS rate at 12 weeks was 12% (3 of 25 pts), median PFS was 9 weeks (IQR 7-11) and median OS 20.7 mts (IQR 14-23). One patient had PSA decline of 30% and another one of 26%, all other had PSA progression. 4 pts (16%) had radiographic progression at week 12. 11 pts (44%) had grade 1 and two pts each grade 2 (8%) or grade 3 (8%) gastrointestinal toxicity (nausea, diarrhoea).

Conclusions: The addition of Met to Abi in pts with mCRPC after PSA progression on Abi did not have a substantial impact on PFS or PSA response. Toxicity of Met in combination with Abi was higher than expected.

Clinical trial identification: NCT01677897

Legal entity responsible for the study: Michael Mark

Funding: Janssen

Disclosure: S. Gillessen, R. Cathomas: Advisor for the Janssen on advisory boards. All other authors have declared no conflicts of interest.

799P Steroid switch: Reversal of resistance to abirateron acetate (AA) and prednisolone (P) combination in metastatic castration-resistant prostate cancer (mCRPC) patients

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Background: AA+P has shown to improve overall survival (OS) in large, randomized trial in the treatment of mCRPC both in pre and post-docetaxel setting. AA is a steroidal CYP17A1 inhibitor, which suppresses androgen synthesis. Because of secondary mineralocorticoid excess it is licensed in combination with P.

Methods: Based on previous data reporting responses following steroid switch upon progression during AA+P a prospective study in mCRPC pts was started. (Lorente at al BJC (2014) 111, 2248–2253).

Results: 23 mCRPC pts were treated with AA (1000 mg q.d.) and P (5 mg b.i.d). Pts characteristics were as follows: median age 73 (95% CI 69-77) years, median Gleason score 8 (7-9), time-span since diagnosis was median 5.6 (3.6-7.8) yrs and all pts. had previous docetaxel treatment and received concomitant androgen deprivation treatment. Pts were on AA+P therapy for median 11.4 (6.4-19.8) mos. In case of PSA progression steroid switch has been applied to dexamethasone (D) (0.5 mg q.d). The PSA progression-free survival on AA+D combination was 5 (3.7-5) mos. 13 (57%) pts are still on AA+D treatment. The OS for AA was 53 (39-53) mos.

Table: 799P

Schedule		PSA progression-free survival (mos)	PSA (ng/ml) at start	PSA (ng/ml) nadir
AA+P	Median	11.4	99	32.5
	95% CI	6.4 -19.8	30-129	13-98
AA+D	Median	5	52	41.5
	95% CI	3.7 - 5	27-133	20-100

During AA+P therapy >25% decrease in PSA occurred in 65% of pts and further decrease (>25%, compared to the nadir during AA+P treatment) has been seen in 26% pts during AA+D treatment.

Conclusions: D can induce further response during AA therapy by reversing glucocorticoid receptor activation or by superior activity of D administered even as a single agent. Our data supports that steroid switch may induce further PSA regression.

Legal entity responsible for the study: Fruzsina Gyergyay

Funding: None

Disclosure: All authors have declared no conflicts of interest.

800P Phase II study of prednisone-dexamethasone switch in metastatic castration resistant prostate cancer (mCRPC) patients treated with abiraterone and prednisone (AA+P)

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Background: Abiraterone Acetate (AA) improves overall survival in mCRPC patients. It is administered with prednisone (P) to decrease the adverse events derived from CYP171A supression. In phase I/II of AA without steroids, dexamethasone (D) 0.5mg/day was added after biochemical progression reaching a 25% of PSA decline. In a retrospective post-docetaxel cohort, Lorente et al (BJC,2014) reported that the switch induced durable biochemical responses in 40% of cases.

Methods: This is a multicentre-prospective phase II study. Its primary aim was to evaluate the antitumour activity of the change of concomitant P 5mg/12h to D 0.5mg/24h daily in mCRPC patients with biochemical and/or limited radiological progression after ≥12 weeks of AA+P treatment. Biochemical response and progression free survival (bPFS) were evaluated by PCWG2 criteria. Radiological response and PFS (rPFS) were evaluated after 12 weeks by RECIST and PCWG2 criteria. Using a single-stage ÁHern Phase II design a minimum of 6 PSA responses >30% in 25 enrolled patients were required to accept the alternative hypothesis (α:5%, 1-β:80%). PTEN and TMPRSS2-ERG in archival tumour-biopsies, AR aberrations in ctDNA and AR-V7 in exosomal RNA were evaluated. The Kaplan-Meier curves were used to calculate survival outcomes.

Results: 26 patients were included. Their clinical characteristics are shown in Table 1. No new safety concerns were observed with AA+D. A decline in PSA≥30% and ≥50% were observed in 12 (46%) and 8 (35%) patients, respectively; two radiological responses were observed; bPFS and rPFS after P to D switch were 4.2 months (CI 95% 2.2-6.2) and 11.8 months (CI 95% 6.9-16.8), respectively.

Table: 800P

Characteristics	AA+D pre-CT (n = 14) N %	AA+D post-CT N %
Age Median (range)	72.9 60-85	72.9 66-78
Baseline PSA Median (range)	26.6 4.5-367	39.9 6.9-1880
Gleason 6-7 8-10 UK	5 36 8 57 1 7	6 50 6 50
ECOG 0-1 2	13 80 1 7	12 100
Metastases Bone Nodes Visceral	12 86 8 57 1 7	12 100 4 33 3 25

Conclusions: In selected clinically stable mCRPC patients the P to D switch as adjuvant of AA could be an acceptable and active therapeutic option. Biomarkers correlation with P to D switch benefit will be reported.

Clinical trial identification: NCT02928432

Legal entity responsible for the study: Spanish National Cancer Research Centre (CNIO)

Funding: Spanish National Cancer Research Centre (CNIO)

Disclosure: D. Lorente Estelles: Speaker fees and advisory boards: Janssen. All other authors have declared no conflicts of interest.

801P Effect of sequence on outcome of prostate cancer patients: retrospective study of a French cohort

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Background: several drugs are approved in prostate cancer (PC), both in localized and metastatic setting. Challenge of daily practice is the sequencing of available agents for optimal disease management. Trying to extract actionable information from the overall history of disease for each patient remains a difficult task but could provide new insights for better sequencing. This retrospective analysis aimed to follow-up patients included in the Rising-PSA phase 3 clinical trial (R-PSA-CP-03) until death or last contact.

Methods: we retrospectively analyzed therapies received by pts included in R-PSA at the HEGP hospital (Paris, France). Drugs were coded in 8 categories: LH: LHRH modulators, AA: anti-androgens, AA2: new generation AA, DC: docetaxel, CZ: cabazitaxel, EX: blinded experimental drugs, P: therapeutic pause, PCB: placebo(experimental). Sequence rank, therapy duration and their interaction was estimated using both a conditional repeated events model (CREM) and a multi-state model (MSM) based on Markov process stratified on disease setting. Covariables included in the models were: age and Gleason score at inclusion time.

Results: 152 pts included between 01/2003 and 09/2007 were followed > 10years. Metastatic progression: 70(46%). Death: 31(20%). Median age(y): 64(51-80)), Gleason ≥8: 47(31%). Median (range) number of sequences received: M0=8(1-15) & M1=6(1-19) including pauses. Number of times each therapy was used whatever the sequence (%M0/%M1): LH(48/10), AA(6/6), AA2(0/22), DC(10/10), CZ (0/10), EX(1/6), PCB(0/2), P(35/34). Upon CREM, the overall model fitted perfectly well the time on therapies and their sequence (robust estimation: $p < 0{,}00001$). Main effects were mostly related to docetaxel, cabazitaxel and experimental drugs in the metastatic setting. Effect of sequence was significant but no therapy x sequence interaction proved to be significant. Comparable results were obtained upon MSM and will be presented.

Conclusions: to our knowledge, this is the first attempt to model the entire course of PC taking into account both therapies and sequence. Given the complexity of our model, these results should be validated with further studies and methods.

Clinical trial identification: R-PSA-CP-03

Legal entity responsible for the study: ARTIC

Funding: None

Disclosure: All authors have declared no conflicts of interest.

802P Patient preference between Cabazitaxel and Docetaxel for first-line chemotherapy in metastatic castrate-resistant prostate cancer (mCRPC): Results from the CABADOC randomized trial

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Background: Docetaxel and cabazitaxel are taxane chemotherapy approved in men with mCRPC after they demonstrated improved overall survival in first- and second-line, respectively. Recent data suggested similar efficacy when used in the first-line setting (Sartor O, ASCO 2016). These two taxanes have different safety profiles. Assessing patient preference between docetaxel and cabazitaxel would contribute to further differentiate between these two agents.

Methods: The CABADOC study is a randomized trial with a cross-over design. Patients with mCRPC were randomized in a 1:1 ratio to receive either docetaxel 75mg/m2/q3w x 4 followed by cabazitaxel 25mg/m2/q3w x 4, or the reverse sequence. Randomisation was stratified based on prior abiraterone or enzalutamide. The primary endpoint was patient preference between taxanes, assessed in patients who had received at least one cycle of each taxane and who had not experienced a progression after the first taxane. Prescott's test was used to analyze the primary endpoint taking into consideration the period effects.

Results: From June 2014 to October 2016, 195 patients were randomized in 17 centers. The median age was 70 years and the median PSA was 49 ng/mL. Patients received 3.8 ± 0.7 and 3.2 ± 1.5 cycles of chemotherapy during the first and the second period, respectively. The eligible population for the primary endpoint comprised 150 patients (45 patients were ineligible for the primary endpoint as per protocol). Among them, 66 preferred cabazitaxel (44% $IC_{95\%}$ = [36-52]), 40 preferred docetaxel (27% $IC_{95\%}$ = [20-34]), and 44 expressed no preference between taxanes (29% $IC_{95\%}$ = [22-37]) ($p = 0.009$). A greater proportion of patients preferred the first received taxane

(44%, $IC_{95\%}$ = [36-52]) versus the second taxane (27%, $IC_{95\%}$ = [20-34]), or had no preference (29% $IC_{95\%}$ = [22-37]). Less fatigue and improved quality of life were the two main reasons provided by patients for their choice. There were 3 toxicity-related deaths (1.5%). Pharmaco-economic analysis, toxicity, and quality of life data will be presented.

Conclusions: A higher proportion of men with mCRPC who are candidates to receive a taxane prefer cabazitaxel over docetaxel.

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Legal entity responsible for the study: Gustave Roussy

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803P Indirect comparison of abiraterone acetate and docetaxel for treatment of metastatic "hormone-sensitive" prostate cancer

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Background: Androgen deprivation therapy (ADT) with or without chemotherapy (docetaxel [DOC]) is recommended in the clinical guidelines as the mainstay of management for metastatic "hormone-sensitive" prostate cancer (mHSPC). The LATITUDE trial demonstrated the efficacy of abiraterone acetate in combination with prednisone and ADT (ADT+AA+P) vs ADT in newly diagnosed mHSPC pts with high-risk disease (NDx HRD). We performed an indirect comparison to determine the relative efficacy of AA vs DOC in mHSPC.

Methods: We conducted a systematic literature review of randomized controlled trials (RCTs) of treatments for mHSPC. To increase comparability of results across studies, the population of interest from LATITUDE and DOC studies was restricted to men with NDx HRD and/or high volume disease (NDx HVD). Two RCTs (CHAARTED, GETUG-AFU 15), both evaluating ADT vs DOC+ADT, met the inclusion criteria. Fixed effects Bayesian network meta-analyses (NMAs) were performed to estimate the relative treatment effects for ADT+AA+P vs DOC+ADT on overall survival (OS) and radiographic progression-free survival (rPFS). The HVD subgroup of LATITUDE was used in the main analysis. The LATITUDE ITT population (NDx HRD) was included as a sensitivity analysis. As STAMPEDE did not report an NDx HVD/HRD subgroup, its M1 population was included in a sensitivity analysis.

Results: The results for HRD/HVD suggested improvement with ADT+AA+P vs DOC+ADT in OS (HR 0.84) and in rPFS (HR 0.73), with Bayesian probabilities (P) for ADT+AA+P 86.8% (OS) and 99.2% (rPFS) more effective. Main results were consistent with all sensitivity analysis results (Table).

Conclusions: Our analyses suggest that ADT+AA+P has greater reduction in risk of progression and death vs ADT+DOC. In absence of head-to-head trials, indirect comparisons based on Bayesian NMA can provide useful insights to clinicians and reimbursement decision makers on the relative efficacy of treatment options for men with mHSPC.

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804P Practice patterns in metastatic castration-resistant prostate cancer (mCRPC): Evidence from the veterans health administration

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Background: Practice patterns for metastatic castration-resistant prostate cancer (mCRPC) have evolved over the last decade due to introduction of agents such as abiraterone and enzalutamide. This study examines mCRPC treatment practices over a 10-year period (which includes the time periods before and after the introduction of novel oral anti-androgens) for the first 3 lines of therapy in the largest nationwide integrated health system in the United States, the Veterans Health Administration.

Methods: By linking patient information from the Veterans Affairs (VA) Clinical Cancer Registry to clinical notes, laboratory, procedure and imaging data from the VA Corporate Data Warehouse (CDW), we identified patients who were diagnosed with prostate cancer at the VA and ultimately developed mCRPC, defined as radiological evidence of metastasis and evidence of rising PSA levels concomitant with surgical (bilateral orchiectomy) or medical castrate testosterone levels ($\leq$ 50 ng/dL within the last 3 months or ongoing treatment with androgen deprivation). Therapies used to treat mCRPC were extracted from CDW pharmacy dispensation records (docetaxel, abiraterone, enzalutamide, cabazitaxel, and others).

Results: From 2006 to 2015, 120,374 patients were diagnosed with prostate cancer, of whom 3,637 developed mCRPC. Median age at initial prostate diagnosis was 68 years (range, 41-94), average BMI was 26.5 (range, 9-59), average CCI score was 1.5 (range, 0-12) and average PSA was 45.5 ng/mL. Practices for the first 3 lines of treatment from 2006 to 2010 and 2011 to 2016 are summarized in Table 1. Patients diagnosed with mCRPC between 2006 and 2010 were more likely to receive cytotoxic therapy than patients diagnosed between 2011 and 2016 (37% vs 22%). Compared with the cohort diagnosed between 2006 and 2010, the later cohort was more likely to receive treatment

Table: 803P

	ADT+AA+P vs ADT		ADT+DOC vs ADT			ADT+AA+P vs ADT+DOC	
	LATITUDE		CHAARTED	GETUG- AFU 15	STAMPEDE		
	HVD & HRD	HRD (ITT)	HVD	HVD	M1	HR [95%-CrI]	$P_{AA>DOC}$
Main analysis							
OS	X		X	X		0.84 [0.63, 1.14]	86.8%
rPFS	X			X		0.73 [0.57, 0.94]	99.2%
Sensitivity analysis							
OS		X	X	X		0.92 [0.69, 1.23]	72.2%
OS	X		X	X	X	0.79 [0.61, 1.03]	96.0%
rPFS		X		X		0.80 [0.63, 1.02]	96.6%

Table: 804P

	ENTIRE COHORT[a] (2006-2016) N = 3,637	mCRPC Diagnosis (2006-2010) N = 1,118	mCRPC Diagnosis (2011-2016) N = 2,519
1L, % pts 2L, % pts 3L, % pts	DOC 27%, AA 22%, ENZ 6% AA 13%, ENZ 10%, DOC 4% ENZ 6%, DOC 4%, AA 3%	DOC 37%, AA 4%, ENZ 1% AA 7%, MIT 5%, CAB 3% AA 3%, ENZ 2%, DOC 2%	AA 29%, DOC 22%, ENZ 9% AA 15%, ENZ 14%, DOC 6% ENZ 8%, DOC 5%, AA 3%
No treatment, % pts	1L 43%, 2L 68%, 3L 86%	1L 56%, 2L 80%, 3L 90%	1L 38%, 2L 63%, 3L 81%
Top 3 most common treatment sequences from 1L to 2L (% of pts)	DOC-AA (11%) AA-ENZ (8%) AA-DOC (4%)	DOC-AA (7%) DOC-MIT (5%) DOC-CAB (3%)	DOC-AA (12%) AA-ENZ (11%) AA-DOC (5%)

AA, abiraterone acetate; CAB, cabazitaxel; DOC, docetaxel; ENZ, enzalutamide; MIT, mitoxantrone [a]<15 patients were treated with radium-223 dichloride or sipuleucel-T

(44% vs 62%) and was also more likely to receive > 1 line of therapy (20% vs 37%). For patients diagnosed between 2011 and 2016, the most common therapies were as follows: 1L, abiraterone (29%); 2L, abiraterone (15%) and enzalutamide (14%); and 3L, enzalutamide (8%).

Conclusions: Our study is the first to describe adoption of non-chemotherapeutic treatments in a nationwide cohort of patients with mCRPC treated in the largest integrated healthcare system in the United States. Further research will focus on understanding clinical outcomes associated with this shift in practice patterns.

Legal entity responsible for the study: Ahmad Halwani, MD

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805P Efficacy and safety of first-line combined androgen blockade in advanced prostate cancer: A meta-analysis

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Background: Combined androgen blockade (CAB) is one of the therapies for advanced prostate cancer. In this analysis, we compared the efficacy and safety of first-line CAB with castration monotherapy in advanced prostate cancer patients.

Methods: The meta-analysis was PRISMA compliant and was registered in PROSPERO (CRD42016054301). We searched PubMed, EMBASE, Cochrane and Scholar for randomized controlled trials (RCTs) published through 12th December 2016 and compared efficacy and safety of first line CAB vs. luteinizing hormone releasing hormone agonists (LHRHa) monotherapy/orchiectomy in advanced prostate cancer. Overall survival (OS) and progression free survival (PFS) were the primary outcomes (fixed/random effects model). Safety was the secondary outcome. Sub-group analyses included: i) Eastern vs. Western patients; ii) non-steroidal anti-androgen (NSAA) vs. steroidal anti-androgen (SAA). Studies with reported HR/presenting median survival and JADAD score >2 were included.

Results: We identified 16 studies (6084 patients; West-12; East-4) for inclusion. CAB treatment significantly improved the OS (14 RCTS; HR 0.90; 95% CI 0.84 to 0.97, P = 0.003) and PFS (13 RCTs; HR 0.89; 95% CI 0.80 to 1.00, P = 0.04) in advanced prostate cancer patients, compared with monotherapy. No significant difference in OS (P = 0.71) and PFS (P = 0.49) was observed between Western vs. Eastern patients. CAB with NSAA significantly improved OS (HR 0.88; 95% CI 0.82 to 0.95, P = 0.0009) and PFS (HR 0.85; 95% CI 0.73 to 0.98, P = 0.007); whereas, CAB with SAA reported similar OS (HR 1.03; 95% CI 0.86 to 1.25, P = 0.74) or PFS (HR 1.01; 95% CI 0.87 to 1.17, P = 0.74) compared with castration monotherapy. Incidence of grade 3 or 4 AEs was not significantly different between CAB and castration monotherapy (P = 0.1083).

Conclusions: First-line CAB therapy significantly improved OS and PFS in advanced prostate cancer patients, with no significant difference in grade 3 or 4 AEs compared with castration monotherapy.

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Funding: AstraZeneca

Disclosure: All authors have declared no conflicts of interest.

806P Outcomes of prechemotherapy (pCRx) abiraterone acetate (AA) or enzalutamide (E) for metastatic castration-resistant prostate cancer (mCRPC) after ADT + Docetaxel (D) or ADT alone for metastatic hormone sensitive prostate cancer (mHSPC) in a multi-institution hospital-based registry

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Background: The E3805: CHAARTED trial noted that the addition of D to ADT was associated with a hazard ratio (HR) of 0.56 (95% confidence interval [CI], 0.44 to 0.70; P < 0.001) for time to CRPC and resulted in a prolongation of overall survival (OS). Therefore, we postulated that pCRx AA or E had greater activity after ADT+D compared to after ADT alone.

Methods: A cohort of mCRPC patients (pts) treated with pCRx AA or E for mCRPC between 2014 and 2017 was identified from three hospitals' IRB approved databases. Patients were grouped by use of D for mHSPC. This time frame was chosen as ADT+D became a valid therapeutic option for mHSPC in 2014 and thus time to pCRx and follow-up were short. The endpoints included OS (time to death from all causes) from ADT start, time to AA/E start from ADT start, and OS from AA/E start. Survival outcomes were analyzed by Kaplan-Meier method.

Results: Of the 102 identified, 50 (49%) had previously received ADT alone, while 52 (51%) had ADT+D. No statistically significant difference in OS from ADT start or from AA/E start was observed between the 2 cohorts (Table 1). Notably, survival in both groups from ADT start was shorter than commonly reported. Yet, deaths in the ADT+D group were 12 vs. 21 in the ADT alone, after a median follow-up of 24.4 and 29.8 months, respectively.

Table: 806P

pCRx AA/E	N (%)	N Deaths (median follow-up mo)	Median OS from ADT start (95% CI mo)	P-value	Time to AA/E start (95% CI mo)	P-value	Median OS from AA/E start (95% CI mo)	P-value
ADT	50 (49%)	21 (29.8)	33.5 (22.4 – NR)	0.2047	11.0 (8.5 – 13.7)	0.7265	17.3 (13.7 – NR)	0.6514
ADT+D	52 (51%)	12 (24.4)	NR (NR-NR)		12.8 (11.1 – 15.7)		NR (13.1 – NR)	

Conclusions: In a cohort of ADT/ADT+D treated mCRPC pts with short times to pCRx AA/E and follow-up, the efficacy of AA/E is similar regardless of previous use of D. It is possible that the pts selected for ADT+D had poorer prognostic factors and yet still did at least as well with AA/E and deaths were lesser. Larger sample sizes, longer follow-up, and better characterization of patient and tumor factors are needed to assess the efficacy of different sequences.

Legal entity responsible for the study: Edoardo Francini

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807P First interim results of the radium-223 (Ra-223) REASSURE observational study: Analysis of patient (Pt) characteristics and safety by use of abiraterone and/or enzalutamide (Abi/Enza)

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Background: Ra-223 prolongs survival with a favorable safety profile in metastatic castration-resistant prostate cancer (mCRPC). The pivotal phase 3 ALSYMPCA trial had a relatively short 3-year follow-up and was conducted before availability of 2nd generation hormonal agents. The REASSURE study was designed to assess long-term safety (7 years follow-up) and conducted in an era when pts had access to other effective 1st line agents such as abi/enza.

Methods: REASSURE is a global, prospective, single-arm, observational study that enrolled pts with mCRPC with bone metastases planned to start Ra-223. Treatment decision was made independently before enrollment. We undertook a planned interim descriptive analysis of safety and drug completion based on prior or concomitant abi/enza use.

Results: REASSURE enrolled 1106 pts in N. America and Europe from Sep 2014 to Sep 2016. The interim analysis included 583 pts who received ≥1 Ra-223 dose (Table; median 7 months observation). Prior abi/enza use was reported in 168 (29%) and concomitant in 153 (26%) pts. Treatment-related adverse events (TRAEs) occurred in 37%: prior abi/enza 45%, no prior abi/enza 34%; concomitant abi/enza 29%, no concomitant abi/enza 40%. TRAEs were most often gastrointestinal or hematological, with permanent discontinuation of Ra-223 in 6%: prior abi/enza 8%, no prior abi/enza 5%; concomitant abi/enza 5%, no concomitant abi/enza 7%. Serious TRAEs (mostly hematologic) occurred in 4.5% leading to permanent Ra-223 discontinuation in 1.5%.

Table: 807P Baseline characteristics and treatment completion by prior or concomitant* abi/enza

	Prior Yes (n = 168)	Prior No (n = 415)	Concomitant Yes (n = 153)	Concomitant No (n = 430)
ECOG 0–1, n (%)	122 (73)	329 (79)	121 (79)	330 (77)
No. of metastases**, n (%)				
<6	42 (26)	123 (32)	53 (37)	112 (28)
6–20	81 (51)	221 (58)	86 (60)	216 (54)
>20	39 (24)	67 (17)	27 (19)	79 (20)
Superscan	14 (9)	21 (5)	5 (3)	30 (8)
ALP (U/L), median	155	115	114	134
<140 U/L, n (%)	58 (35)	153 (37)	54 (35)	157 (37)
≥140 U/L, n (%)	73 (43)	126 (30)	51 (33)	148 (34)
PSA (ng/mL), median	136	43	43	76
LDH (U/L)***, median	327	260	291	264
Prior docetaxel or cabazitaxel, n (%)	96 (57)	100 (24)	46 (30)	150 (35)
Completed 5 or 6 Ra-223 doses, n (%)	87 (52)	282 (68)	106 (69)	263 (61)

*Prior = abi/enza stopped before starting Ra-223. Concomitant = any overlap with Ra-223.
**Pts undergoing more than one imaging modality may be reported in multiple categories.
***LDH was available for 209/583 patients.

Conclusions: Ra-223 has a good short-term safety profile when used in the routine clinical practice setting. Prior or concomitant abi/enza does not appear to increase TRAE incidence. Pts who had prior abi/enza had a lower rate of completing full Ra-223 dosing, perhaps reflecting poorer prognosis or more advanced disease as suggested by higher median PSA and LDH levels.

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Legal entity responsible for the study: Bayer Healthcare

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808P A phase II study of enzalutamide (Enz) with dutasteride (Dut) or finasteride (Fin) in men ≥ 65 years with hormone-naive systemic prostate cancer (HNSPCa)

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Background: Older men are at risk for adverse events (AEs) from androgen deprivation therapy (ADT). In prior studies, peripheral androgen blockade with bicalutamide and Fin was better tolerated but less efficacious than ADT in HNSPCa. The potential synergism of Enz and Dut/Fin provided the rationale for this Phase II study.

Methods: Eligible subjects were ≥ 65 yrs; at risk of AEs from ADT as determined by treating physicians; had metastatic (M1) or non-metastatic (M0) HNSPCa with a PSA doubling time <9 months; and had testosterone >50 ng/dl. Enz (160mg daily) with Dut (0.5mg daily) or Fin (5mg daily) was given until progression per the Prostate Cancer Working Group 2 guidelines or unacceptable AEs. Comprehensive geriatric assessment (CGA) was done at baseline and every 4 months. The primary endpoint is time to PSA progression. The secondary endpoints are time to PSA nadir, AEs, and effects on CGA domains.

Results: As of 4/15/17, we completed study enrollment of 40 subjects. Herein, we report outcomes of the first 31 subjects with a median follow-up of 43 weeks. Median age at enrollment was 80 yrs. 29%, 61%, and 10% had ECOG performance status of 0, 1, and 2, respectively. 45% had M0 and 55% had M1 HNSPCa. Gleason's sum was 6, 7, >8, and unknown in 19%, 49%, 23%, and 9%, respectively. At enrollment; the median PSA was 12.71 ng/ml. CGA showed cognitive impairment in 61%, physical impairment in 54%, depression in 16% and impairment of instrumental activities of daily living in 13%. The median time to 90% PSA decline was 7 weeks. 79% of patients had 80% DHT decline by 9 months. At the time of analysis, all patients had PSA decline of > 90% without radiographic evidence of disease progression. Baseline CGA did not correlate with efficacy (P-values >0.1). Common Grade 1 AEs included gynecomastia (26%), fatigue (35%), hot flashes (22%) and paresthesia (13%). None had Grade 3 or 4 AEs. Three men withdrew from the study due to treatment-related AEs (Grade 2 fatigue and paresthesia). Another three patients withdrew due to unrelated issues.

Conclusions: Enz with Dut/Fin appears to be safe and efficacious for older patients with M0 and M1 HNSPCa. Future research will report effects of treatment on CGA domains.

Clinical trial identification: NCT02213107

Legal entity responsible for the study: University of Rochester

Funding: Astellas and Pfizer Inc

Disclosure: All authors have declared no conflicts of interest.

809P Cabazitaxel plus prednisone and prophylaxis of neutropenia complications in the treatment of metastatic castration-resistant prostate cancer after failure to docetaxel: A multicenter, non-comparative, open-label, phase IV study

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Background: This study aimed to evaluate the effectiveness of granulocyte colony-stimulating factor (G-CSF) and ciprofloxacin in the prophylaxis of hematological complications in mCRPC patients treated with cabazitaxel after docetaxel failure and at risk for neutropenia.

Methods: Phase IV, non-randomized, open-label, single-arm interventional study, with men aged ≥65 years (or < 65 years and 25% irradiated bone marrow), presenting mCPRC after docetaxel failure, ECOG status ≤1, life expectancy >12 weeks, that provided informed consent. Cabazitaxel 25 mg/m^2 was given with prednisone on day1 every 21 days. G-CSF was administered on days 2 to 8 of each cycle or until ANC >2,000/mm^3 and ciprofloxacin 1000mg on days 5 to 12. Primary endpoint was the rate of neutropenia grade ≥3 during the first cycle; secondary endpoints were the rate of neutropenia grade ≥3, febrile neutropenia, diarrhea grade ≥3, PSA response and quality of life (FACT-P) during treatment. Statistical significance was set at 0.05 and 95% confidence intervals were determined.

Results: 46 patients with median age 71.5 years (mean: 71.8 years) and 69.0 months on median since diagnosis (mean: 75.2 months) of prostatic cancer were included. Among the 45 treated patients, exposed to a median of 9.0 cycles (mean: 9.5 cycles) during 210 days, 40.0% (95% CI, 25.7%-54.3%) presented one episode of neutropenia grade ≥3 during the first cycle. During treatment, 42.2% patients presented at least one neutropenia grade ≥3; febrile neutropenia occurred in one patient (2.2%) as well as diarrhea grade ≥3. Twenty-nine patients (64.4%) achieved PSA response and 77.2% improved FACT-P score in at least one visit. Three patients (6.7%) had a serious TEAEs leading to death (none related to treatment), and 13.3% had 7 TEAEs leading to treatment discontinuation (3 related to treatment).

Conclusions: Prophylactic G-CSF and ciprofloxacin was effective in the prevention of neutropenia grade ≥3 and other hematological complications during the mCRPC treatment with cabazitaxel 25 mg/m^2 in patients who were at risk for neutropenia.

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Legal entity responsible for the study: Sanofi

Funding: Sanofi

Disclosure: F.C. Maluf: Speaker at Sanofi-Aventis, Janssen, Bayer, AstraZeneca, Astellas, Ferring, Ache. Clinical trial investigator at Sanofi-Aventis, GSK, Janssen, Astellas, Bayer. Member of advisory board at Sanofi-Aventis, Janssen, Bayer, Astellas. F.A.M. de Oliveira: Speaker at Janssen. P.E.R. Liedke: Grants from Roche, Pfizer, Sanofi. L. Brust: Advisory Board Boheringer, Janssen, Agendia. F.S.M. Monteiro: Speaker at Sanofi, BMS, Pfizer, Janssen, Astellas e Merck Serono. Advisory Board at Janssen. Chair LACOG GU (Latin America Cooperative Oncology Group - Genito–Urinary Tumors). All other authors have declared no conflicts of interest.

810P Assessment of health-related quality of life (HRQL) in PROSELICA: A Phase 3 trial assessing cabazitaxel 20 mg/m2 (C20) vs 25 mg/m2 (C25) in post-docetaxel (D) patients (pts) with metastatic castration-resistant prostate cancer (mCRPC)

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Background: PROSELICA (NCT01308580) assessed effect of C20 vs C25 on overall survival in a non-inferiority study of pts with mCRPC. Primary analyses included assessment of HRQL in the overall population. Post-hoc subgroup analyses investigated changes in HRQL in pts receiving C20 vs C25 according to median treatment cycles received (6).

Methods: Functional Assessment of Cancer Therapy Prostate (FACT-P) was used to assess HRQL. The least square means of change in FACT-P total score (TS) from baseline (BL) was assessed via a mixed-effect model for repeated measurements and differences were compared for C20 vs C25 in pts receiving > 6 or ≤ 6 treatment cycles.

Results: Overall change in FACT-P TS from BL to Cycle 10 was not significantly different for C20 vs C25 (C20 n = 137: 0.02 [95% confidence interval [CI] -2.57, 2.61]; C25 n = 141: 1.33 [95% CI -1.26, 3.93]; p = 0.369). For evaluable pts who received > 6

cycles, change in FACT-P TS from BL to Cycle 10 favored C25 but not C20 (C25 n = 140: 3.06 [95% CI 0.25, 5.86], p = 0.033; C20 n = 137: 2.67 [95% CI -0.17, 5.51], p = 0.065). Difference in change was not significant for C20 vs C25 (-0.39 [95% CI: -3.66, 2.88], p = 0.816). For evaluable pts who received ≤ 6 cycles, change in FACT-P TS from BL to Cycle 6 favored pts receiving C25 (C25 n = 49: -4.61 [95% CI: -8.27, -0.95], p = 0.014; C20 n = 39: -6.58 [95% CI: -10.46, -2.69], p < 0.001) but the difference between the treatment arms was not significant (-1.96 [95% CI: -6.8, 2.87], p = 0.426). Increasing cycles, BL ECOG performance score (0–1 vs ≥ 2) and receiving > 6 cycles significantly improved FACT-P TS change from BL (p < 0.001). Difference in treatment dose (C20 vs C25) did not have a significant effect on FACT-P TS change from BL (p = 0.354).

Conclusions: In the overall population, HRQL did not differ significantly from BL to Cycle 10 for C20 vs C25. Additionally, there were no significant differences between the two treatment arms (C20 vs C25) in either subgroup (> 6 or ≤ 6 cycles). A significant change in HRQL from BL to Cycle 10 was observed in patients who received > 6 cycles of C25. Funding: Sanofi.

Clinical trial identification: NCT01308580

Legal entity responsible for the study: Sanofi

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811P Cabazitaxel followed by androgen deprivation therapy (ADT) significantly improves time to progression in patients with newly diagnosed metastatic hormone sensitive prostate cancer (mHSPC): A randomized, open label, phase III, multicenter trial

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Background: Patients with newly diagnosed mHSPC have a poor prognosis with a 3-year overall survival (OS) rate of 50%. Recently, combination of docetaxel (75mg/m2 every 6 weeks for 6 cycles) with ADT has become a new standard for such patients, based on results of 2 large phase 3 trials showing a significant OS benefit. In these trials, docetaxel was initiated within 3 months after ADT start. Timing of ADT and chemotherapy (CT) is controversial. In breast cancer, endocrine therapy is always started after CT, the rational being that ADT will turn clones of tumor cells in to a stage of dormancy where CT is less effective.

Methods: This phase 3 trial randomized newly diagnosed mHSPC patients to receive cabazitaxel (CABA), 25 mg/m2 every 3 weeks for 10 cycles, followed by ADT (immediately after last CABA cycle) versus ADT alone. Primary end-point was OS. Secondary end-point was progression free survival. The study planned to include 400 patients but was closed prematurely due to low inclusion rate. A total 31 patients with newly diagnosed mHSPC were included and here we present the results.

Results: Median follow up was 31 month. Of the CABA treated patients, 66.8% got six cycles or more and 46.7% completed all 10 courses. Median OS was 32,5 months with CABA followed by ADT and 29,5 months with ADT alone (HR 1.43, 95% CI 0.38-5.38). Median progression free survival was significantly longer in CABA treated patients (29 vs 12 months, HR 3.96 (95% CI 1.49-10.49). Main grade ≥ 3 toxicities were neutropenia (66%).

Conclusions: In conclusion, results from this prematurely terminated trial suggest that CABA followed by ADT is effective in newly diagnosed mHSPC and shows a manageable toxicity. These results have to be validated in larger randomized trials.

Clinical trial identification: NCT01978873

Legal entity responsible for the study: Department of Urology, Orebro University Hospital, Sweden

Funding: Sanofi aventis

Disclosure: All authors have declared no conflicts of interest.

812P Health-related quality of life (HRQL) in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) treated with cabazitaxel (CBZ) in a prospective observational study (CAPRISTANA)

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Background: Cabazitaxel (CBZ) is a taxane approved for mCRPC treatment post docetaxel based on Phase 3 clinical trial data. Observational studies are in progress to gather information on real-world treatment patterns, safety, efficacy and HRQL effect of CBZ outside of clinical trials.

Methods: The prospective, observational study CAPRISTANA evaluated the routine clinical use of CBZ (25 mg/m^2 every 3 weeks plus prednisone 10 mg/day) in pts with mCRPC previously treated with docetaxel. HRQL was assessed using Functional Assessment of Cancer Therapy - Prostate (FACT-P) version 4 and EQ-5D-3L (including VAS - visual analogue scale) questionnaires at baseline and every two cycles until CBZ discontinuation.

Results: A total of 192 pts were treated in 55 centers across 6 countries (Apr 2012–Jun 2016); 161 and 157 pts were evaluable for FACT-P and EQ-5D, respectively. Pts received 6 (median) cycles of CBZ (range 1–24); 53.6% achieved disease control with CBZ. The main reason for CBZ treatment discontinuation was disease progression (58.3%). No new safety signals were identified. In the overall FACT-P score analysis, HRQL improvement during CBZ treatment was recorded in 31.8%, no change in HRQL in 40.4%, and deterioration was recorded in 27.8% of pts. The highest rate of improvement was observed for the Prostate-Specific Concerns subscale (49.3%) and Pain Control subscale (54.2%). The highest rate of deterioration was recorded for the Functional Well-Being subscale (40.9%). Mean FACT-P score and EQ-5D health utility index and VAS scores did not show statistically significant changes during CBZ treatment.

Conclusions: In this real-world study investigating HRQL associated with the use of CBZ in pts with mCRPC, no significant changes were observed in mean on-treatment FACT-P score and EQ-5D scores. However, in contrast to observations in prospective clinical studies, pts had improvement in the Pain Control FACT-P subscale. These results suggest that, in addition to the previously demonstrated effectiveness, CBZ treatment may help pts to achieve better pain control.

Legal entity responsible for the study: Sanofi

Funding: Sanofi

Disclosure: G. Barnes: Employee of Sanofi. M. Ghosn: Advisory boards for Sanofi, Astellas and Janssen. I. Koroleva: Research funding and speakers' bureau for AstraZeneca and Teva, travel reimbursement from MSD and Eisai. A. Ozatilgan: Employee of Sanofi. S. Hitier: Employee of Sanofi. J. Carles: Consulting/advisory role to Johnson&Johnson, Bayer, Astellas, BMS, Pfizer and Sanofi. All other authors have declared no conflicts of interest.

813P Real-world use of docetaxel for metastatic castration-resistant prostate cancer in China: Results from a large observational study

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Background: This study investigated real-world patterns of docetaxel use for metastatic castration-resistant prostate cancer (mCRPC) in China.

Table: 813P

Pattern of use of docetaxel in Chinese patients with mCRPC	n (%)	Median overall survival, months (95% CI)	PSA response rate, % (n/n[a])
All patients	403 (100)	22.4 (20.4, 25.8)	70.9 (168/237)
After failure of 1st-line hormonal therapy	170 (42.2)	22.5 (19.2, 29.5)[b]	73.6 (64/87)
After failure of 2nd-line hormonal therapy	125 (31.0)	23.3 (18.1, 26.5)[b]	67.1 (55/82)
After failure of ≥ 3rd-line hormonal therapy	51 (12.7)	22.4 (19.0, 36.5)	65.4 (17/26)
After failure of estramustine therapy	46 (11.4)	20.2 (16.6, 27.7)	69.7 (23/33)
Other	11 (2.7)	28.6 (17.5, not evaluable)	100.0 (9/9)

[a]Denominator is the number of patients in each category who had PSA ≥20 ng/ml at baseline;
[b]p = 0.781 for median overall survival with initiation of docetaxel following failure of 1st- and 2nd-line hormonal therapy. mCRPC, metastatic castration-resistant prostate cancer; PSA, prostate specific antigen.

Methods: A prospective, multi-centre, observational study of Chinese adults (≥18 years) with histologically confirmed metastatic prostate adenocarcinoma who received ≥1 dose of docetaxel following hormonal therapy failure (disease progression and serum testosterone <50 ng/dL). The primary endpoint was patterns of docetaxel use. Secondary endpoints included median overall survival (mOS), prostate-specific antigen (PSA) response rate (RR) and reasons for docetaxel discontinuation. Variables are summarised as mean (SD) unless specified. All patients provided written informed consent.

Results: From August 2011 to June 2016, 403 patients were enrolled at 32 centres and 315 (78.2%) completed the study. The mean number of docetaxel cycles and dose were 4.4 (2.86) and 66.9 mg/m2 (9.12), and treatment compliance was 94.0% (10.94%). mOS was similar for docetaxel after 1st- or 2nd-line hormonal therapy (Table), and was longer in patients without visceral metastases versus those with visceral metastases (23.3 months vs. 17.4 months, P = 0.019). Planned docetaxel treatment was completed by 30.8% (124) of patients; the most common reasons for discontinuation were 'other reasons' (23.3% [94]), cost of medical expenses (22.6% [91]), and tumor progression (14.1% [57]). Treatment-emergent AEs (TEAEs) occurred in 20.8% (84), and serious TEAEs in 4% (16), of patients.

Conclusions: Around three-quarters of Chinese mCRPC patients treated with docetaxel initiate treatment after failure of 1st- or 2nd-line hormonal therapy and mOS and PSA RR are similar in both settings. Docetaxel was relatively well tolerated.

Legal entity responsible for the study: Sanofi-Aventis

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Disclosure: All authors have declared no conflicts of interest.

814P Longer time from diagnosis to docetaxel treatment results in a shorter survival in metastatic hormonosensitive prostate cancer (mHSPC) patients treated with chemotherapy+androgen deprivation therapy (ADT)

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Background: Addition of 6 cycles of docetaxel to ADT prolongs survival and is the standard treatment for mHSPC based on results of Chaarted and Stampede trials. Prognostic factors have not been clearly described for these patients. A retrospective analysis of clinical and pathological prognostic factors was performed in 76 patients from 5 academic institutions.

Methods: Retrospective analysis of all (n = 76) mHSPC from 5 Spanish Oncology Centres was performed. All patients had been treated with docetaxel + ADT as first line. Clinical and pathological variables were analyzed: age, Gleason (6-7 vs 8-10), presence of visceral metastases, number of bone metastases (0,1-4,5-20,>20), PSA value at diagnosis and previous to CT, PSA response previous to CT (>25%, 25-50%, 50-100% or no response), time from diagnosis to first docetaxel treatment (>or< 50days). Progression free (PFS) and overall survival (OS) were the endpoints analyzed by log-rank test.

Results: Median PFS was 17m and median OS has not been reached (80% of patients alive at 20 months). Median follow-up: 16.6m. Median age 64,3y (range: 46-80), median PSA at diagnosis 691ng/mL (range:15235-1), median PSA previous to CT 214ng/mL (range:5060-0), PSA responses to ADT previous to CT was 25% in 35 pts (46%), 25-50% in 14 pts (18.4%), less than 50% in 13 (17.2%), no response in 14 (18.4%), Gleason 6-7: 19 (25%), 8-10: 53 (69,7%), UK 3 (5.3%). Median time from diagnosis to docetaxel 45.3 d (range 0-167). PFS nor OS was related to age, PSA at diagnosis, PSA response prior to docetaxel or Gleason. Time from diagnosis to docetaxel (p = 0.04) (median 21 vs 15m; HR:2.2)) and Gleason (median not reached vs 15m; HR: 3.3) were statistically significant factors for PFS. Presence of visceral metastasis (p = 0.08) (20m vs median not reached;HR: 3.8) and time from diagnosis to docetaxel (p = 0.02) (median not reached vs 24m; HR:4.1) were significative factors for OS.

Conclusions: A time from diagnosis to docetaxel start longer than 50 days is associated with lower PFS and OS in m+HSPC patients treated with ADT + docetaxel. Gleason ≥ 8 score correlates with shorter PFS and the presence of visceral metastases with a lower OS.

Legal entity responsible for the study: Dr. Miguel A. Climent Durán

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Disclosure: All authors have declared no conflicts of interest.

815P Prognostic value of systemic inflammatory biomarkers in patients with mCRPC treated with abiraterone in pre-docetaxel setting

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Background: Systemic inflammatory biomarkers have shown a prognostic impact in several solid tumors. The aim of this study was to examine the prognostic role of baseline neutrophil-to-lymphocyte-ratio (NLR), platelet-to-lymphocyte-ratio (PLR) and lymphocyte-to-monocyte-ratio (LMR) and NLR, PLR and LMR changes at 1, 2 and 3 months in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) treated with Abiraterone Acetate (AA) in pre-docetaxel setting.

Methods: We retrospectively included mCRPC pts treated with AA at two Italian hospitals from November 2012 to April 2017. NLR, PLR and LMR were evaluated at baseline and after 1, 2 and 3 months of treatment. The impact of NLR, PLR and LMR on progression-free survival (PFS) was evaluated by Cox regression analyses both in univariate and multivariate fashion. Other clinico-pathological factors, such as PSA baseline level, Time to CRPC, Gleason Score, Presence of Visceral Metastases and Bone Metastases Burden were included.

Results: Fifty mCRPC pts treated with AA were evaluated. At univariate analysis, elevated baseline NLR and PLR were significantly associated with shorter median PFS (p = 0.01, hazard ratio [HR]=1.224 and p = 0.0001, HR = 1.013 respectively); after 1

month of treatment, NLR and PLR were significantly predictors of worst PFS (p = 0.03, HR = 1.320 and p = 0.02, HR = 1.012 respectively). After 2 and 3 months of treatment, only high PLR was associated with poor prognosis (p = 0.01, HR = 1.012 at month 2; p = 0.009, HR = 1.009 at month 3 respectively). LMR didn't show any prognostic relevance. At multivariate analysis, only baseline PLR was independently associated with PFS (p = 0.006, HR = 1.013).

Conclusions: High baseline and early-assessed NLR and PLR during treatment with AA are associated with shorter PFS in mCRPC pts. PLR more than NLR may be considered as an early and easy-to-perform prognostic marker in this setting.

Legal entity responsible for the study: Fondazione IRCCS Istituto Nazionale dei Tumori of Milan

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816P 68Ga-PSMA-PET/CT as a changing practice tool in biochemically recurrent prostate cancer

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Background: PSMA-PET/CT have demonstrated interesting results in the detection of loco-regional and distant disease in prostate cancer patients with biochemical relapse. Even with low levels of PSA, PSMA imaging is able to identify metastatic lesions, being a possible tool for tailoring treatment decisions. This study aims to describe the use of PSMA-PET/CT in the daily practice and its clinical impact in the management of prostate cancer patients who have rising PSA after curative treatment.

Methods: We performed a retrospective analysis in 29 localized prostate cancer patients of three private Brazilian cancer institutions who underwent PSMA-PET/CT for rising PSA after treatment with curative intent. The clinical impact of PSMA-PET/CT was evaluated by whether the assistant physician changed or not the treatment strategy based solely on PSMA results. In addition, modifications related to local (salvage radiotherapy [SRT], salvage lymphadenectomy [SL]) and systemic (antiandrogen deprivation therapy [ADT], chemotherapy [chemo]) treatment were described.

Results: In total, 29 patients were enrolled. Twenty-seven (93%) had undergone radical prostatectomy, and 2 (7%) radiotherapy as the local curative treatment. Sixteen cases (55%) had not received any radiotherapy previously. The mean Gleason score, PSA level and PSADT at time of the examination were 8, 4.2 (0,05-41) ng/ml and 4.4 (0.4-27) months, respectively. PSMA-PET/CT detected at least one suspicious lesion for prostate cancer in 21/29 (58%) patients. Overall, 15/29 (51%) patients had their treatment strategy changed due to results in PSMA imaging. In only 3/29 (10%) the modifications were related exclusively to systemic protocols (1 avoided ADT, 1 added ADT and, 1 added chemo). Whereas in the 12/29 (41%) remaining cases, treatment strategy change involved local treatment. Of these 12 with a local treatment change, 7 added (6 SL, 1 SRT) and 5 avoided (5 SRT) local therapies.

Conclusions: Half of the patients with biochemical relapse that underwent PSMA-PET/CT had their treatment protocol changed, most changes related to local treatment. Although the role of PSMA imaging is not clearly defined, PSMA-PET/CT has been used as a practice changing tool in the daily practice.

Legal entity responsible for the study: Instituto COI

Funding: None

Disclosure: All authors have declared no conflicts of interest.

817P Prostascore: A simplified tool for predicting outcomes among patients with treatment-naïve advanced prostate cancer

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Background: The objective of this study is to propose and validate a new simplified model "prostascore" to help predict the outcomes of treatment-naïve patients with advanced prostate cancer.

Methods: Through SEER*Stat program, surveillance, epidemiology and end results (SEER) database was queried for eligible records spanning the period from 2010 to 2013. Multivariate analysis for the candidate prognostic factors (extent of extra-prostatic disease, PSA level and grade) was conducted through a Cox proportional model. Prostascore was then calculated for each patient. Cancer-specific and overall survival analyses according to prostascore were conducted through Kaplan-Meier analysis/log-rank testing.

Results: A total of 8727 patients with treatment-naïve advanced prostate cancer and complete baseline data were identified in the period from 2010-2013. The following factors were associated with better cancer-specific survival (isolated regional nodal disease, lower PSA level and lower grade group) ($P < 0.0001$). Based on the results of the multivariate analysis, the prostascore was described. A prostascore point was given for each of: PSA level $\geq$ 60 and grade group 4 or 5. The site/distribution of extra-prostatic disease were given the following points: 0 for isolated regional lymph nodes (N1), 1 for non regional lymph deposits (M1a), 2 for bone deposits (M1b) and 3 for other sites (M1c). A total prostascore was then calculated for each case in the cohort (which may range from 0 to 5). After assignment of a prostascore for each patient, cancer-specific and overall survivals were compared according to the score. Pair wise comparisons between all different scores were conducted. For both cancer-specific and overall survival assessment according to the prostascore model, *P* values for pair wise comparisons among different score points were significant ($P<0.0001$). Table-1 shows number of patients and three year cancer-specific survival years according to prostascore.

Table: 817P Distribution and 3-year cancer-specific survival rates for different scores in the evaluated cohort

Score	N(%)	3-year cancer-specific survival rates
0	1024 (11.7%)	98%
1	1639 (18.8%)	97%
2	898 (10.3%)	91%
3	2161 (24.8%)	88%
4	2537 (29.1%)	79%
5	466 (5.4%)	76%

Conclusions: Prostascore is an easy and reliable tool for predicting the outcomes of patients with treatment-naïve advanced prostate cancer. Further validation within the context of other treatment settings and population-based cohorts is recommended.

Legal entity responsible for the study: Omar Abdel-Rahman

Funding: None

Disclosure: All authors have declared no conflicts of interest.

818P PSA doubling time (PSADT) and proximal PSA predict metastasis-free survival (MFS) in men with biochemically recurrent prostate cancer (BRPC) after radical prostatectomy (RP): Implications for patient counseling and clinical trial design

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Background: We previously reported a relationship between PSADT and MFS in BRPC post RP (Pound 1999; Freedland 2007; Antonarakis 2012). In men with PSADT<12 months, who are at high risk of lethal prostate cancer (PCa), we sought to identify a PSA cutpoint (proximal PSA; PP) that indicates the imminent emergence of metastasis (M+). In this report we combined Center for Prostate Disease Research and Johns Hopkins (CPDR/JHU) databases to investigate the association of the PP value on MFS in men with BRPC and PSADT <12 mths.

Methods: In the CPDR/JHU RP database (31,296), 513 men with BCR (>0.2ng/ml) with PSADT <12 mths who received no adjuvant/salvage ADT/RT were prospectively followed until radiological evidence of M+ are included in this analysis. All patients were evaluated yearly with $\geq$1 PSA and scans at regular intervals until M+. Associations with MFS were compared using logrank test and Cox regression. The PP is the most recent value $\geq$6 months prior to M+/censor.

Results: M+ occurred in 218 of 513 patients with BRPC (median follow up 9 years). Risk of M+ increased for PSADT 6.0-7.5, 4.5-6, 3.0-4.5, and $\leq$3.0 months, adjusted for pT stage and Gleason score. PP $\geq$ 10 ng/ml significantly increased risk of M+ in pts with PSADT <12 mths, regardless of PSADT subgroup, hazard ratio=2.736, p<.0001. Table 1 shows median MFS by PP in subgroups with PSADT $\leq$3 mths, 3.01-6 mths, and 6.01-12 mths.

Table: 818P

PSADT	Median metastasis-free survival (year)		
	Proximal PSA<10 ng/mL	Proximal PSA ≥10 ng/mL	P value
6.01-12 mths	20 (n = 277)	5 (n = 64)	<.0001
3.01-6 mths	7 (n = 106)	3 (n = 47)	0.0009
< =3 mths	3 (n = 48)	1 (n = 21)	0.058

*Based on logrank analysis

Conclusions: In men with PSADT<12 months, PSADT subgroups ≤7.5 months and PP ≥ 10ng/ml are independent predictors of MFS, adjusted for pT stage and Gleason score. PP ≥ 10ng/ml further define risk of M+ in BRPC with PSADT<12 months. These data can assist physicians during discussions with patients regarding the risk of developing M1 disease and facilitate clinical trial design in this prevalent group of patients.

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Disclosure: All authors have declared no conflicts of interest.

819P PSA kinetics impact on CT-PET PSMA uptake in prostate cancer

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Background: CT-PET PSMA has recently been approved to more accurately detect the extent of prostate cancer. Here we examined PSA level and kinetics (PSA doubling time-PSADT) as a predictor of positive up-take in patients evaluated for suspected recurrent disease.

Methods: We retrospectively collected data on 99 patients evaluated by CT-PET PSMA. Mann-Whitney U test and student's T Test (SPSS 20) were applied to test for differences in median in PSA and PSADT level, Pearson test was used for correlation analysis. PSADT was calculated by Memorial Sloan Kettering Cancer Center calculator of 3 recent levels.

Results: Ninety nine patients underwent CT-PET PSMA. Their median age was 71 (52-94) years. Uptake was detected in 84 (84.8%) patients; 51 (51.5%) patients with metastatic disease (lymph nodes, bones, visceral) and 33 (33.3%) patients with only localized disease (prostate, prostatic bed after prostatectomy). Median Gleason 8 (6-10), median PSA 4.66 (0.12-272) ng/ml. CT-PET was positive in 57.1%, 88.9% and 96.8% of patients with PSA levels of ≤ 1, >1-2 and >2 ng/ml, respectively, and 91.7%, 90.5% and 81.8% of patients with PSADT ≤2, >2-6 and > 6 months, respectively. Only median PSA levels were significantly associated with any uptake: 5.90 ± 35.71 vs. 0.35 ± 4.18 ng/ml, p < 0.001. Median PSADT, but not PSA, was statistically associated with metastatic disease compared to only local disease: 6.2 ± 13.64 vs. 20.3 ± 130.52 months, p < 0.001. Similar results outcome were obtained using student's t-test (data not shown). Gleason score predicted for CT-PET PSMA metastatic uptake (median 8 vs. 7, p = 0.02). There was no correlation between Gleason score and PSADT (r= -0.197, p = 0.058).

Conclusions: The decision to perform CT-PET PSMA in prostate cancer patients suspected to have recurrent or metastatic disease should be based on PSA levels. PSADT is a significant marker for positive metastatic CT-PET PSMA uptake.

Legal entity responsible for the study: Avishay Sella

Funding: None

Disclosure: All authors have declared no conflicts of interest.

820P Combining functional imaging with circulating biomarker analysis to improve prognostication of metastatic castration-resistant prostate cancer (mCRPC)

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Background: Biomarkers for treatment personalization in mCRPC could improve patient outcomes. Multiple tests on blood have reported associations with worse outcome, including serum lactate dehydrogenase (LDH), chromogranin A (CgA), neutrophil-lymphocyte ratio (NLR) and more recently *AR* copy number (CN) in plasma DNA (Conteduca, Ann Oncol 2017). Biological data suggest an association between choline uptake and androgen receptor (*AR*) expression. We here aimed to integrate 18^{F}-fluorocholine (FCH) uptake on PET/CT with plasma *AR* CN and other routinely obtained circulating biomarkers and evaluate associations with outcome.

Table: 820P Multivariable cox proportional hazard analysis of predictors of progression-free survival and overall survival

	PFS		OS	
	HR (95% CI)	p	HR (95% CI)	p
TLA*				
<563979	1.00		1.00	
≥563979	1.13 (0.50-2.58)	0.762	1.12 (0.44-2.83)	0.809
MTV*				
<112	1.00		1.00	
≥112	0.81 (0.33-2.00)	0.647	0.99 (0.38-2.56)	0.988
SUVmax*				
<50.00	1.00		1.00	
≥50.00	2.04 (0.98-4.23)	0.056	3.38 (1.48-7.68)	0.004
Previous chemotherapy				
No	1.00		1.00	
Yes	0.96 (0.50-1.84)	0.907	0.43 (0.18-1.05)	0.064
CgA*, ng/mL				
≤360	1.00		1.00	
>360	2.63 (1.42-4.87)	0.002	2.08 (1.08-4.00)	0.029
NLR				
<3	1.00		1.00	
≥3	2.00 (1.08-3.68)	0.026	1.99 (1.04-3.82)	0.038
LDH, mU/mL				
<225	1.00		1.00	
≥225	1.50 (0.80-2.80)	0.207	2.15 (1.07-4.34)	0.032
***AR* copy number**				
Normal	1.00		1.00	
Gain	2.62 (1.26-5.47)	0.010	2.15 (1.02-4.52)	0.044
Median dsDNA concentration, ng/mL				
<38.5	1.00		1.00	
≥38.5	0.69 (0.37-1.29)	0.243	1.18 (0.60-2.33)	0.628
After backward stepwise procedure				
***AR* copy number**				
Normal	1.00		1.00	
Gain	2.16 (1.17-4.01)	0.014	2.13 (1.13-4.02)	0.019
SUVmax*				
<50.00	1.00		1.00	
≥50.00	1.91 (1.00-3.64)	0.048	3.06 (1.51-6.23)	0.002
CgA*, ng/mL				
≤360	1.00		1.00	
>360	2.73 (1.51-4.93)	0.0009	2.37 (1.25-4.47)	0.008
NLR				
<3	1.00		1.00	
≥3	1.86 (1.05-3.29)	0.032	2.18 (1.18-4.00)	0.012

*cut-off determined by ROC curve *Abbreviations:* ALP, alkaline phosphatase; AR, androgen receptor; CgA, chromogranin A; CI, confidence interval; dsDNA, double-strandend DNA, ECOG, Eastern Cooperative Oncology Group; FCH PET/CT, 18F-fluorocholine positron emission tomography/computed tomography; HR, hazard ratio; LDH, lactate dehydrogenase; MTV, metabolic tumor volume; NLR, neutrophil-lymphocyte ratio; PS, performance status; PSA, prostate-specific antigen; SUV, standardized uptake value; TLA, total lesion activity.

Methods: We determined plasma *AR* DNA by digital PCR and Taqman from 105 CRPC samples collected before abiraterone (n = 65) or enzalutamide (n = 40). Pre-treatment serum LDH, CgA, NLR were also measured. FCH-PET/CT scan was performed at baseline and SUVmax, total lesion activity (TLA) and metabolic tumor volume (MTV) were calculated. Patients (pts) were dichotomized in high and low according to receiver-operating characteristic (ROC) curves. Main endpoints were the correlation of FCH-PET/CT parameters with circulating biomarkers and their impact on progression-free/overall survival (PFS/OS).

Results: Plasma *AR* CN gain was observed in 27 pts (25.7%) and correlated significantly with high SUVmax ($p < 0.0001$), TLA ($p < 0.0001$), MTV ($p = 0.0006$) and greater number of lesions on FCH-PET/CT ($p < 0.0001$). On multivariable analysis, SUVmax, plasma *AR*, CgA, NLR and LDH were significantly associated with outcome (Table 1).

Conclusions: Choline uptake was significantly related to plasma *AR* CN gain as well as elevated NLR, CgA, and LDH values. This analysis identified independent predictors of survival in mCRPC and more accurate prognostic distinct groups using molecular, laboratory and imaging features. The potential integration of these non-invasive biomarkers could be as a tool for a better treatment selection of CRPC. A larger prospective evaluation is warranted.

Legal entity responsible for the study: Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) Srl – IRCCS.

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821P A polymorphism in the promoter of the FRAS1 gene is associated with metastatic prostate cancer

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Background: Inflammation and one of its mediating transcription factors, NF-kappa B signaling (NFκB) have been implicated in prostate cancer (PrCa) carcinogenesis. We sought to define whether germline gene polymorphisms that interact with NFκB are associated with metastatic disease after prostatectomy (RP) or radiation (XRT) for localized disease.

Methods: Using a bioinformatics approach interrogating publicly available datasets, we defined a genome-wide functional association network specific to lethal PrCa consisting of 351 genes and 8,154,133 high-confidence functional associations related to the NFκB pathway. The dense module searching (DMS) method was used to analyze 419,461 SNPs from a previously conducted genome wide association study (GWAS) case-only study of 196 lethal PrCa cases compared to 368 indolent controls in the Harvard School of Public Heath (HSPH) Cohorts. Top hits from DMS were then tested in two independent PrCa cohorts: (i) ECOG/DFCI (n = 254 cases, 256 controls) and (ii) Fred Hutchinson Cancer Research Center (FH, n = 570 cases, 103 controls). In all 3 studies, "controls" were men with PrCa who are alive with no evidence of metastasis at least 8-years after RP or XRT and "cases" were men who developed metastatic disease after RP or XRT (FH, HSPH, ECOG) or with *de novo* presentation (ECOG).

Results: From the DMS, 40 SNPs with a minor allele frequency > 0.1 were associated with lethal PrCa. Of these, rs1910301 in the promoter region of FRAS1 was nominally associated with lethal disease in all 3 studies with similar size effects: the odds ratio (OR) for the A allele was 1.40 ($p = 0.02$) in HSPH, 1.35 in ECOG/Gelb ($p = 0.04$), and borderline significant in FH [OR 1.3, $p = 0.07$]. Fixed effects meta-analysis of all three cohorts found a significant association: OR = 1.38 95% CI: 1.15-1.66; p-value 0.005.

Conclusions: A SNP in the promoter region of FRAS1, which forms a gene unit with FREM2 and together regulate epidermal-basement membrane adhesion and cell migration, is associated with metastatic PrCa. FREM2 is an NFκB regulated gene and mutations in FREM2 and FRAS1 are associated with the Fraser syndrome. Further work is needed to determine the effect of rs1910301 on FRAS1 function and cellular adhesion and the metastatic process.

Legal entity responsible for the study: Christopher Sweeney

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822P Phenotypic circulating tumor cell (CTC) classifier of genomic instability (GI) associates with improved overall survival (OS) for metastatic castration-resistant prostate cancer (mCRPC) patients (pts) receiving platinum agents in addition to taxanes

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Background: The presence of GI has been associated with DNA Damage Response (DDR) genomics. mCRPC pts with DDR(-) can have treatment (Tx) efficacy with poly ADP ribose polymerase inhibitors (PARPi). Similar Tx benefit for DDR(-) pts has been observed with alkylating agents such as platinum Tx in small cohorts. However, obtaining and sequencing metastatic biopsies is currently not scalable for routine use in the clinic due to accessibility, cost and time to result. We previously developed an imaging-based phenotypic classifier to predict presence of GI from individual CTC morphology and demonstrated that these pts had statistically worse OS when receiving androgen receptor signaling inhibitors (ARSi) or Taxanes. In a separate cohort, the same classifier predicted improved PSA response when pts were treated with a PARPi + ARSi vs. ARSi alone. Here, we examined if GI(+) mCRPC pts can have improved OS when receiving a commonly available and inexpensive platinum chemotherapy.

Methods: 89 blood samples were collected from mCRPC pts prior to taxane Tx (n = 62) or a combination of taxane + platinum (T+P) (n = 27), and processed utilizing the Epic Sciences platform. Choice of therapy was at the discretion of attending physician without knowledge of CTC results. The percent of predicted GI cells per pt sample (%pGI) was calculated after single-cell characterization. Pts were followed for OS.

Results: Pts receiving a T+P combination had higher CTC burdens and lower PSA levels but otherwise showed similar pre-Tx characteristics to taxane-only pts. In a multivariate model containing %pGI, therapy class, and total CTC burden (to help correct for disease burden and severity), a significant interaction between the T+P combination and increasing %pGI, and increased OS (HR: 0.14, CI: 0.026 to 0.72, $p = 0.018$) was observed.

Conclusions: The results of this study suggest that in a prospective setting with a balanced cohort, pts with high %pGI might have improved OS on taxanes with the addition of platinum agents. Propspective validation of the signature is planned.

Legal entity responsible for the study: MSKCC

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823P Expression of steroid hormone transporter, SLCO1B3, is mediated by a CBP/p300 regulatory mechanism in prostate cancer

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Background: Recent studies support the role of steroid hormone transporters in modulating intratumoral androgen concentrations, thereby promoting castration-resistant prostate cancer (CRPC) progression. The organic anion polypeptide 1B3 (OATP1B3) transporter is expressed de novo in prostate tumors and contributes to the transport of androgen into these cells. Polymorphic variations in the SLCO1B3 gene encoding OATP1B3 are related to clinical outcome in men with prostate cancer receiving androgen deprivation therapy (ADT) or those with CRPC. The current study elucidates the mechanism of de novo SLCO1B3 expression in prostate cancer. We discovered that chetomin, a known inhibitor of HIF-1α- and CBP/p300 binding, was a potent inducer of SLCO1B3 transcripts.

Methods: We investigated the transcriptional regulation of SLCO1B3 expression by CBP/p300 using siRNA-mediated gene silencing or treatment with various CBP/p300 inhibitors (C646, HATi II) to determine the effects on gene transcription, downstream pathways, and transporter-dependent uptake studies.

Results: Treatment with various CBP/p300 inhibitors (CH1 or HAT binding domains) significantly increased the expression of SLCO1B3 and subsequent transporter-mediated androgen uptake in tumor cells. Specific downregulation of p300 or CBP by siRNA reduced SLCO1B3 expression in prostate cancer cells (22Rv1, LNCaP, and PC3), suggesting that CBP/p300 interacts with specific transcription factors essential for driving SLCO1B3 expression. Cells treated with ADT elicited differential effects on transporter expression in AR-positive vs AR-null cells. Studies are currently underway to identify cofactors involved in forming the CBP/p300 transcriptional complex regulating SLCO1B3 expression.

Conclusions: *De novo* OATP1B3 expression in prostate cancer is a mechanism of tumoral resistance to ADT resulting in greater androgen uptake. Taken together, the data suggest that ADT resistance and transporter-dependent increased uptake of residual androgens result from CBP/p300-mediated *SLCO1B3* expression. OATP1B3 should be considered a viable biological target for therapeutic intervention in prostate cancer.

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824P ARV7 status and CTC count: A combined biomarker for the baseline therapeutic decision in each line of mCRPC treatment

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Background: Metastatic Castration Resistant Prostate Cancer (mCRPC) is an entity for which we have more than one therapeutic option. Chemotherapy and novel hormonal agents (NHAs) are the main choices. Despite clinical, biochemical, radiological and histologic parameters, we have not yet confirmed the ideal sequence of regimens. Since PSA is not enough to guide treatment selection in mCRPC, there is a need for a biomarker that would lead us to the ideal regimen choice in each line of therapy for each patient (pt) in order to transform mCRPC into a chronic disease. ARV7 status and circulating tumor cells (CTCs) have shown some potential as biomarkers the last 2 years. The aim of this study was to combine these two biomarkers as a parameter for selecting the optimal treatment strategy. We aimed to categorize mCRPC pts by combining ARV7 status and CTC count and correlating this with response to therapy and, consequently, regimen choice.

Methods: CellSearch was used for CTC counts. We developed a highly sensitive and specific multiplex RT-qPCR assay in the LightCycler platform for the simultaneous quantification of AR splice variants (AR-FL, AR-V7, AR-567, AR-total) in CTCs. 41 pts and 57 samples were categorized in four groups: 1. CTChigh(h) (CTC count >10) ARV7 + (14 samples) 2. CTClow(l) (CTCcount < =10) ARV7- (20 samples) 3. CTClARV7 + (14 samples) 4. CTCh ARV7- (9 samples). Treatment choice at this point was independent of ARV7 status and CTC testing and was selected upon treating oncologist's decision.

Results: PSA response to chemotherapy or NHAs was studied for each group, as well as duration of treatment and change of pt classification in groups. In each group, pts were categorized according to treatment type (chemotherapy, NHAs) and PSA responses were categorized as PSA decline or not. Group 1 pts did not appear to respond to NHAs but only to chemotherapy and had a worse prognosis compared to all other groups; pts in group 2 appeared to have an excellent and long term response to NHAs, though if chemo was received they also responded equally to both treatment options and had a better prognosis compared to all other groups; pts in group 3 responded better to chemotherapy than NHAs (though not excluding NHAs as a treatment choice); pts in group 4 responded to chemo and not NHAs.

Conclusions: Pts CTCl and ARV7- could safely be treated with NHAs while CTCl and ARV7+ pts could be treated with either chemotherapy or NHAs, with chemotherapy probably being a "safer" choice (less PSA non responses 1/8 vs 3/6). ARV7+ status does not seem to be an exclusion criteria alone for NHAs use in this category. For CTCh pts, chemotherapy is the best choice especially when pts are ARV7+. Since CTC and ARV7 status can change, these could be used as the baseline biomarker for regimen choice.

Legal entity responsible for the study: Evangelos Bournakis

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Disclosure: All authors have declared no conflicts of interest.

825P Limited value of currently used germline brca mutations predictive tools in prostate cancer

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Background: Germline BRCA1 and BRCA2 mutations have been associated to poor prostate cancer (PrCa) outcomes and may have implications for cancer treatment. Identification of these carriers would also serve for the early identification of other family members at increased risk of breast and ovarian cancer. Several tools have been developed to estimate the probability of a gBRCA mutations in the context of a family history of breast and/or ovarian cancer but its performance has not been evaluated in PrCa patients.

Methods: This is single-centre study aimed to: 1) compare the contribution of PrCa to identify families known to harbour a germline BRCA1 or BRCA2 mutation; and 2) estimate the ability of predicting a BRCA mutation in these families based on the cancer history at the time of PrCa diagnosis. A comprehensive reassessment of families attending our Familial Cancer screening program at Málaga Univ. Hospitals between 2012-16 identified 104 families known to harbour a gBRCA mutations. gBRCA mutation risk estimations were calculated with 2 commonly used risk assessment models: BRCAPRO 6.0 and Manchester Score (MS).

Results: Finally, a total of 98 families (42 BRCA1, 56 BRCA2) were included in the study, after exclusion for further analyses of families with PrCa cases in non-carriers (phenocopies). As expected, PrCa was more common in BRCA2 carriers (2 vs 19, $p = 0.002$). Median age of PrCa diagnosis was 70 yrs (48-83). Male breast cancer was more common in families with PrCa (24% vs 4% $p = 0.003$), particularly in BRCA2 families (26.3% vs 5.4%, $p = 0.023$), but no other differences in family history of cancer were observed between families with or without PrCa cases and therefore their scores using BRACAPRO and MS did not differ. A $\geq$ 10% probability of finding a BRCA2 mutation was identified in 47% of families using BRCAPRO, decreasing to 21% when the proband was the PrCa patient ($p = 0.002$). Similar results were observed when the probability was calculated using MS (42% vs 21%, $p = 0.011$)

Conclusions: The currently available predictive tools underestimate the probability of a BRCA mutation when the proband is a prostate cancer patient and should not be used as unique tools to decide which PrCa patients should undergo genetic testing.

Legal entity responsible for the study: Institutod e Investigación Biomédica en Málaga (IBIMA)

Funding: Asociación para el apoyod e la Investigación O

Disclosure: All authors have declared no conflicts of interest.

826P Prevalence and baseline clinico-pathological associations of germline deleterious mutations in DNA repair genes (gmDDR) in a metastatic castration resistant prostate cancer (mCRPC) prospective spanish cohort (PROREPAIR-B study)

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Background: DNA repair has been reported as a frequent altered pathway in mCRPC. The prevalence of gmDDR has been recently estimated in a retrospective pooled analysis of 7 UK-US institutions as 11.8% in mCRPC (Pritchard, NEJM 2016). However, geographic differences are expected and its association with the phenotype of mCPRC in other populations remains unknown.

Methods: PROREPAIR-B study is a prospective multicenter observational cohort study. Blood samples and clinical data have been collected prospectively in 38 centres across Spain. Germline DNA was extracted from EDTA blood samples using Flexigene®. Sequencing libraries were generated from 250ng of gDNA using a custom panel of 124 genes related to DNA repair and familial cancer, with the NimbleGen SeqCap XL Target Enrichment (Roche®) tecnhology. Validation of pathogenic mutations by Sanger, MLPA or additional NGS has been performed only for 24 genes included in the BROCA panel. Preliminary statistical analyses have been conducted comparing clinico-pathological characteristics at diagnosis and at mCRPC between carriers and non-carriers.

Results: 38 validated gmDDR were detected in 419 patients (9.1%), with 5 additional cases undergoing further validation studies. BRCA2 was the most frequently mutated gene (n = 14) followed by ATM (n = 8), BRCA1 (n = 4) and CHEK2 (n = 4). Characteristics at prostate cancer diagnosis (dx): 99% caucasian; median age 66y (41-92); Gleason <7 41% vs ≥ 8 59%; localized stage 35% vs stage IV 65%. Characteristics at mCPRC dx: median age 73y (43-94); ECOG 0-1 91% vs 2 9%; presence of visceral 8%, bone 87% and lymph node metastasis 46%; median baseline PSA 26.95ng/ul (<0.02-5198). Bone metastases were significantly more common at mCRPC dx in carriers (95% vs 80%, p = 0.04), as well as ALP>2*UNL (37% vs 19%, p = 0.03) and Albumine < 4g/dl (45% vs 21%, p = 0.02). No significant differences were observed between carriers and non-carriers in age at dx or mCRPC, Gleason, stage at dx, PSA, LDH, Hemoglobin, visceral or nodal metastases at mCRPC dx (p > 0.05).

Conclusions: This is the first study that reports the prevalence of gmDDR in a cohort of mediterranean mCRPC patients.

Clinical trial identification: NCT03075735

Legal entity responsible for the study: Spanish National Cancer Research Centre (CNIO)

Funding: Spanish National Cancer Research Centre (CNIO)

Disclosure: All authors have declared no conflicts of interest.

827P Comprehensive characterization of BRCA1 and BRCA2 alterations in circulating tumor DNA and tumor tissue in men with prostate cancer: Implications for clinical care

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Background: Alterations in genes encoding for DNA damage repair (DDR) such as BRCA1 or 2 – as detected by next generation sequencing (NGS) – can predict for sensitivity to PARP inhibitors or platinum-based chemotherapy in advanced prostate cancer (PC). Detection of these alterations either in tumor tissue or in circulating tumor DNA (ctDNA) in men with advanced PC is clinically actionable in certain clinical contexts. Previously, we reported the comprehensive molecular characterization of DNA DDR genes in 936 unique primary & metastatic PC specimens (Dall'era, ASCO GU 2017) where 24.4% had at least 1 mutation in a DNA repair gene. We also reported that DNA DDR alterations were more common in metastatic vs. localized disease. We sought to expand this work by employing NGS in ctDNA as part of clinical care to ascertain the mutational status of BRCA1 and 2 in men with PC.

Methods: The nature and prevalence of BRCA1 and 2 alterations in ctDNA were determined from 207 men with PC through the Foundation ACT NGS assay. Mean depth of coverage was 6963x. Similarly, BRCA1/2 alterations in 936 unique PC specimens were assessed as part of the Foundation One NGS assay. Mean depth of coverage was >500X.

Results: In ctDNA specimens from 207 patients, 15 (7.2%) arboured known or likely deleterious BRCA1 (n = 4) and/or BRCA2 (n = 12) alterations consisting of 19 short variants and 2 rearrangements. One case had 4 variants in BRCA2 while 3 cases had 3 variants, of which 1 case had both BRCA1 and 2 variants. An additional 17 ctDNA cases (8.2%) arboured BRCA1/2 alterations categorized as variants of unknown significance (VUS). In the 936 tumor specimens, 118 (12%) had known or likely deleterious BRCA1 (n = 11) or BRCA2 (n = 107) alterations consisting of 4 rearrangements, 89 short variants, and 30 copy number variants. VUS were not available for tumor specimens.

Conclusions: Potentially actionable BRCA1 and/or BRCA2 alterations are detectable in ctDNA or tumor tissue in up to 15% of men with PC in this large dataset of specimens obtained in the course of clinical care. Employing plasma-based ctDNA NGS provides a clinically convenient means for assessing the status of DNA gene repair alterations comparable to that of tumor tissue.

Legal entity responsible for the study: University of California Davis Comprehensive Cancer Center and Foundation Medicine

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Disclosure: R. Hartmaier, S.M. Ali: Employee of Foundation Medicine. All other authors have declared no conflicts of interest.

828P Durable prostate cancer control in a randomized trial of optimal timing of dose escalated (76 Gy) radiation and 6 months ADT in prostate cancer

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Background: A pooled analysis of trials using conventional dose radiation (XRT) indicates 6 months androgen deprivation therapy (ADT) improves prostate cancer survival in Gleason 7 disease (D'Amico, JCO 2011). The benefit of ADT when used in combination with dose escalated XRT remains controversial. In EORTC 22991 trial 6 months ADT improved disease free survival at all XRT dose levels (Bolla, JCO 2016). We present long-term results of dose escalated XRT (76 Gy) in combination with 6 months ADT in the context of a Phase 3 Trial evaluating the optimal timing of ADT in combination with XRT.

Methods: 438 pts were entered on the trial. Inclusion criteria were cT1-T3, Gleason < 8, PSA < 30. Low risk pts were excluded. ADT consisted of 6 mo Total Androgen Blockade (TAB) with Goserelin and Biclutamide. Pts were randomized to upfront XRT (day 1 of ADT) or XRT after 4 months ADT. Median follow-up is 12 yrs. 10 yr overall Survival (OS), Cause Specific Survival (CSS) PSA Disease Free Survival (DFS) and Local DFS were estimated using Kaplan-Meier (KM) method.

Results: Clinical characteristics are as follows: mean age 69; 69% cT1-T2A, 31% cT2B-T3; 75% Gleason 7; mean PSA = 10. Protocol compliance: 96% of pts completed 6 mo TAB and 99% completed 6 mo Goserelin. 4% of patients stopped Biclutamide early (3% due to Grade 1-3 reversible liver toxicity). 4% of patients developed late Gr 3 proctitis. 10 yr results: PSA DFS 83%, CSS 98%, OS 76%, and local DFS 95%. The results by treatment arm will be presented in the near future.

Conclusions: The durable DFS, local control and CSS support the benefit of 6 mo ADT in combination with Dose Escalated (76 Gy) XRT. The favourable compliance, tolerance and toxicity data support this treatment approach. Potential survival benefits of ADT in intermediate risk prostate cancer will be evaluated by mature results from EORTC 22991 and RTOG 0815 trials.

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Legal entity responsible for the study: Ottawa Hospital Research Institute

Funding: None

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829P Initial results from AQUARiUS, a prospective, observational, multicentre phase IV study assessing patient-reported outcomes (PROs) in metastatic castration-resistant prostate cancer (mCRPC) patients (pts) treated with abiraterone acetate plus prednisone (AAP) or enzalutamide (ENZ)

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Background: AQUARiUS is an ongoing study evaluating PROs and medical resource use in 2 cohorts of chemotherapy naïve mCRPC pts newly initiated on AAP or ENZ in the real-world setting.

Methods: The study prospectively collects PROs on quality of life, cognition, fatigue and pain using EORTC QLQ-C30, FACT-Cog, BFI-SF and BPI-SF questionnaires, respectively, for 12 months (mo) in 211 pts. This analysis describes PRO data for pts with 3-mo follow-up (N = 105). Multivariate repeated measures linear and logistic

Table: 829P Mean change in score from baseline for AAP (N = 46) vs ENZ (N = 59) Interpretation of the PRO items: for FACT-Cog and QLQ-C30 higher scores are favourable, for BFI-SF lower scores are favourable

PRO item	Month 1				Month 2				Month 3			
	AAP Mean (n*)	ENZ Mean (n*)	Score difference (95% CI)†	P value	AAP Mean (n*)	ENZ Mean (n*)	Score difference (95% CI)†	P value	AAP Mean (n*)	ENZ Mean (n*)	Score difference (95% CI)†	P value
Perceived cognitive impairments range 0-72 (FACT-Cog)	2.1 (42)	−2.7 (53)	4.77 (1.26, 8.29)	0.008	1.4 (34)	−5.4 (41)	6.65 (2.79, 10.51)	< 0.001	1.1 (25)	−5.9 (37)	6.97 (1.16, 12.79)	0.020
Cognitive functioning range 0-100 (QLQ-C30)	2.4 (41)	−5.7 (53)	6.01 (0.47, 11.55)	0.034	2.6 (32)	−8.3 (42)	9.48 (2.73, 16.24)	0.007	−0.6 (26)	−14.9 (38)	11.95 (0.74, 23.15)	0.037
Your usual level of fatigue range 0-10 (BFI-SF)	−0.4 (41)	0.3 (54)	−0.58 (-1.43, 0.27)	0.179	−0.6 (33)	0.7 (42)	-1.20 (-2.14, -0.26)	0.014	−0.7 (26)	1.0 (35)	−1.58 (-2.90, -0.25)	0.021
Fatigue interference range 0-10(BFI-SF)	−0.1 (42)	0.0 (53)	−0.38 (-1.10, 0.35)	0.308	−0.4 (34)	0.2 (42)	-0.99 (-1.82, -0.15)	0.021	−0.2 (26)	0.7 (35)	−1.32 (-2.41, -0.22)	0.019
Clinically meaningful worsening (vs improvement or no change) for AAP (N = 46) vs ENZ (N = 59) Defined as the difference from baseline ≥ minimal important difference (0.5 x SD of baseline PRO of all pts)												
PRO item	Month 1				Month 2				Month 3			
	AAP % (n*)	ENZ % (n*)	Odds ratio (95% CI)	P value	AAP % (n*)	ENZ % (n*)	Odds ratio (95% CI)	P value	AAP % (n*)	ENZ % (n*)	Odds ratio (95% CI)	P value
Perceived cognitive impairments (FACT-Cog)	7 (42)	34 (53)	0.15 (0.04, 0.56)	0.005	6 (34)	49 (41)	0.07 (0.02, 0.28)	< 0.001	8 (25)	38 (37)	0.16 (0.03, 0.76)	0.021

*Evaluable pts

†Regression model estimates Note: 7 pts (2 AAP, 5 ENZ) included in this intention-to-treat analysis switched treatment within the first 3 months; results were consistent in the per protocol analysis and censoring analysis.

regression models were used to analyse change from baseline scores and risk for clinically meaningful worsening, respectively, adjusting for baseline characteristics.

Results: Baseline characteristics were well balanced between the ENZ (N = 59) and AAP (N = 46) cohorts. PRO items with significant differences ($p < 0.05$) between the 2 cohorts consistent across time points on continuous and/or binary endpoints are reported in the table. Change from baseline comparisons favour AAP over ENZ for mo 1, 2 and 3 for perceived cognitive impairments (e.g., 1.1 vs -5.9 at mo 3) and cognitive functioning (e.g., -0.6 vs -14.9 at mo 3) and for mo 2 and 3 for usual level and interference of fatigue (e.g., -0.7 vs 1.0 and -0.2 vs 0.7 at mo 3). Within the first 3 mo ENZ-treated pts had a significantly higher risk of experiencing clinically meaningful worsening in perceived cognitive impairments vs AAP-treated pts.

Conclusions: Initial results suggest favourable outcomes for perceived cognitive impairments and functioning, and fatigue for AAP vs ENZ within the first 3 months after treatment initiation.

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Legal entity responsible for the study: Janssen Pharmaceutica N.V.

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830P Assessment of association between clinical characteristics and prostate specific antigen (PSA) progression in men with prostate cancer (PCa) receiving a leuprorelin acetate implant: Results from the non-interventional German cohort LEAN study

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Background: The impact of GnRH (gonadotropin-releasing hormone) therapy on comorbidities and lifestyle is complex but important to consider in men with PCa. The LEAN study aims to analyse associations between various anamnestic factors and PSA dynamics in men with advanced, hormone-dependent PCa receiving a leuprorelin acetate solid implant (Leuprorelin Sandoz®/Leuprone® HEXAL®).

Methods: Patients were enrolled at 190 German centres from January 2014. Metabolic data, body measures, PSA and testosterone were assessed at baseline and during 1-year follow-up. Cox model analyses assessed associations between anamnestic factors and PSA progression. Data are presented as mean±standard deviations.

Results: A total of 959 patients have been recruited. Median patient age was 75 years (range 50–93; ≥65: 90%) and median body mass index (BMI) was 28 kg/m^2 (range: 18–49; >30: 22%). Primary diagnosis of PCa was 26±47 months before inclusion, with PSA levels of 32±53 ng/mL [median: 11] and serum testosterone of 3.6±2.16 ng/mL [median: 3.5]. Six of the 12 (median) core biopsies were positive at primary diagnosis, with a Gleason Score of 7.5±1.2 (median: 7). A total of 189 patients (27%) had previous radical prostatectomy 29±50 days (median: 7) before inclusion. Over 50% of patients had concomitant cardiovascular disease and 16% had disorders of glucose or lipid metabolism. At 3, 6, 9 and 12 months after the start of leuprorelin therapy, median PSA values decreased to 0.6, 0.3, 0.2 and 0.2 ng/mL, respectively, and median testosterone levels were 0.2, 0.2, 0.2 and 0.2 ng/mL. PSA progression occurred in 168 patients: in

28% of patients with BMI ≤30 and in 26% with BMI >30, indicating no clear association with BMI (p = 0.7427). Cox model analyses also showed no clear influence on PSA progression of other anamnestic factors.

Conclusions: Patients in the LEAN study represent a real-life population receiving therapy with a GnRH agonist. Results show no clear influence of anamnestic factors on PSA progression.

Clinical trial identification: DRKS00005643

Legal entity responsible for the study: N/A

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Disclosure: B. Schmitz-Dräger: Consultant or assessor: Hexal, Janssen, Amgen Fees: Hexal, Janssen, Myriad, Astellas. S. Mühlich: Consultant or assessor: Hexal Fees: Hexal, Janssen, Medac. B. Ottillinger: Consultant or assessor: Hexal Fees: Hexal Employment or position of leadership: Hexal. M. Studen: Holder of shares, stocks or funds: Hexal, Amgen Employment or position of leadership: Hexal.

831P Neuropsychiatric adverse events of enzalutamide and abiraterone acetate plus prednisone treatment: Contrasting a meta-analysis of randomized clinical trials with real world reporting patterns from EUDRA

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Background: Enzalutamide (ENZ) and abiraterone acetate plus prednisone (AAP) are oral antiandrogens indicated in Europe [1] for the treatment of metastatic castration resistant prostate cancer (mCPRC). A comparative preliminary analysis of cognitive decline and mood changes in mCRPC patients receiving ENZ and AAP has been reported[2]. However, a meta-analysis for these adverse effects (AEs) has not been available in the literature.

Methods: Following on from the methodology presented by Ruiz et al.[3] a further meta-analysis was performed to estimate the pooled Relative Risk (RR) of neuropsychiatric AEs for AAP and ENZ. A complementary analysis of the EUDRA database was performed to explore the consistency of the real world adverse drug reactions (ADR) reporting pattern with the meta-analysis.Calculation of Proportional Reporting Ratios was performed following EUDRA guidelines.

Results: The meta-analysis results indicate that patients treated with ENZ had a statistically significant higher risk of restless leg syndrome, anxiety, headache and insomnia vs control (Table). Both ENZ and AAP showed increased significant risk for falls vs control. The Proportional Reporting Ratio (PRR)[4] of suspected ADRs reported in EUDRA is higher with ENZ than with AAP for all the variables analyzed.

Conclusions: The analysis suggests that some neuropsychiatric AEs are more prevalent with ENZ vs placebo than AAP vs prednisone. The reporting trend in EUDRA is consistent with this result.

Legal entity responsible for the study: Janssen

Funding: Janssen-Cilag

Disclosure: M. Sanchez Iznaola: Market access manager at Janssen Pharmaceuticals in Spain. R. Parra: Group Manager Hemar lead in onco-hematology at Janssen Pharmaceuticals in Spain. G. Angela: Medical affairs lead in oncology at Janssen Pharmaceuticals in Spain. J. Casariego: Medical affairs Director for solid tumors for Janssen Emea. J. Muñoz Del Toro: Medical affairs in oncology at Janssen Pharmaceuticals in Spain. P. Robinson: Hemar lead in oncology for Janssen Emea.

832P Influence of an international consensus conference on practice patterns in advanced prostate cancer (APC)

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Background: Development of several agents and combinations in metastatic castrate-naïve (mCN) and castration-resistant (mCR) PC has led to uncertainty in best management approaches. The Advanced Prostate Cancer Consensus Conference (APCCC) 2017 convened to provide expert opinions on open questions.

Methods: 57 questions (Qs) selected from a sample of consensus Qs to be voted on at APCCC 2017 were administered as a pre- and post-conference survey to attendees. Matched responses before and after APCCC 2017 were compared to identify changes in attendees' treatment preferences in APC.

Results: From 2/2017-4/2017, pre- and post-conference surveys from 120 attendees were collected mostly from medical oncologists (41.7%) and urologists (40.8%). Attendees reached a consensus ≥75% vote in the same pre- and post-meeting question in 10/57 Qs (15.7%). A < 75% consensus vote to ≥ 75% vote (or vice-versa) change was seen in 3 key areas: abiraterone or enzalumatide was more favored as first-line option in patients (pts) who progressed on docetaxel ≤6 months in CNPC (60.0% pre- to 75.9% post-meeting), 2 years was the favored duration of osteoclast-targeted therapy in mCRPC (53.3% to 75.0%), and more next-generation imaging (MRI or PET/CT) was favored in mCRPC (12.7% to 24.1%) while CT and bone scan changed from 79.7% to 70.7% of votes. Consensus ≥75% votes was not reached in the majority of Qs, but notably there were more post-conference votes for: using a lower dose of cabazitaxel 20 mg/m^2 vs 25 mg/m^2 (24.2% to 32.8%), carboplatin in refractory mCRPC with DNA repair defects (27.5% to 42.2%), adding ADT to salvage XRT (29.1% to 49.1%), ≤3 metastases as a definition for oligometastatic PC (48.7% to 70.8%), recognition of ADT causing bone loss/fractures (57.4% to 66.4%), vitamin D + calcium in pts on ADT (62.6% to 71.7%), and osteoclast-targeted therapy in pts on ADT with osteopenia/osteoporosis (42.6% to 59.3%).

Conclusions: To the best of our knowledge, we are among the first to compare pre- and post-meeting responses that highlight interesting changes in provider preferences in APC management. Consensus conferences such as APCCC where expert opinions are discussed provide a unique learning experience and delineate key areas of controversy in APC where further study is needed.

Legal entity responsible for the study: The Advanced Prostate Cancer Consensus Conference

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Table: 831P

	Source	n	Headache	Seizures	Falls	Dizziness	Hallucinations	Restless leg syndrome	Memory impairment	Anxiety	Insomnia
AAP	COU-AA 301 & 302 Pooled RR (95%CI)	2267	1,12 (0,89-1,40)	1.0 (0.09-10,95)	1,60 (1,03-2,49)*	0.97 (0,77-1,23)	-	-	-	1,04 (0,78-1,64)	1,04 (0,83-1,30)
AAP	EUDRA ADRs Feb 17 (PRR)[4]	7498	29 (0,49)	18 (0,22)	57 (0,51)	56 (0,45)	6 (0,29)	2 (0,24)	5 (0,15)	6 (0,21)	10 (0,21)
ENZ	PREVAIL & AFFIRM Pooled RR (95%CI)	2914	1.7 (1.31-2.19) *	2,20 (0,39-12,39)	2,30 (1,67-3,17)*	1,21 (0,86-1,76)	4,74 (0,76-29,67)	5,87 (2,05-16,78)*	1,21 (0,86-1,76)	1,52 (1,04-2,23)*	1,45 (1,09-1,91)*
ENZ	EUDRA ADRs Feb 17	24258	197 (2,10)	258 (4,69)	383 (2,04)	414 (2,29)	66 (3,4)	29 (4,48)	111 (6,86)	92 (4,73)	159 (4,91)

*p < 0,05

833P Postoperative radiation therapy after radical prostatectomy

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Background: To analize the results of adjuvant and salvage radiotherapy after radical prostatectomy and to determine prognostic factors of biochemical relapse free survival (BRFS).

Methods: 302 patients were treated at our institution over a 12-year period. Overall survival and biochemical-relapse free survival were calculated using Kaplan-Meier and multivariate Cox regression analysis was used to assess differences between groups.

Results: Mean age at diagnosis was 65 years (42-80). All patients underwent radical prostatectomy combined with pelvic lymphadenectomy in 47.1% of cases. Adjuvant RT was performed in 113 patients and salvage RT in 183 (9 for local recurrence). The distribution of patients by pT stage was pT2a-b(30.3%), pT2c (35%), pT3(29%) and pT4(2.3%). Upgrade in Gleason score between biopsy and prostatectomy was experienced by 46.7% of patients. Positive surgical margins were reported in 56.5% of cases. Neoadjuvant androgen ablation before surgery was given to 36.5%. Mean pre-RT PSA of 0.46ng/ml (0-12.8) and mean dosis to surgical bed was of 70Gy (60-76Gy). Mean follow-up was 58.85 months (1-153 months). Overall survival at 5 and 10 years was 98.1% and 94.3%, respectively and BRFS at 5 and 10 years was 76.5% vs. 61.8%, respectively. The timing of RT (ART vs. SRT) and pre-RT PSA <0.5 ng/ml were significant predictors of longer BRFS.

Conclusions: Postoperative radiation therapy provides excellent long-term overall survival with an aceptable BRFS. Pre-RT PSA <0.5ng/ml and adjuvant RT were predictors of better outcomes.

Legal entity responsible for the study: Hospital Ramón y Cajal

Funding: None

Disclosure: All authors have declared no conflicts of interest.

834TiP Randomized phase III trial of ipatasertib vs. placebo, plus abiraterone and prednisone/prednisolone, in men with asymptomatic or mildly symptomatic previously untreated metastatic castrate-resistant prostate cancer (mCRPC)

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Background: In a Phase Ib/II study, the small-molecule AKT inhibitor ipatasertib in combination with abiraterone and prednisone/prednisolone demonstrated an improved radiographic progression-free survival (rPFS) vs abiraterone and prednisone/prednisolone alone, with greater benefit in patients with phosphatase and tensin homolog (PTEN)–loss tumors. This randomized Phase III trial will evaluate the efficacy, safety and pharmacokinetics (PK) of ipatasertib vs placebo (both combined with abiraterone and prednisone/prednisolone) in patients with previously untreated mCRPC.

Trial design: Eligible patients must have untreated asymptomatic or mildly symptomatic mCRPC with progressive disease by Prostate Cancer Clinical Trials Working Group 3 criteria, ongoing androgen deprivation therapy or castrated state and ECOG PS 0 or 1. Treatments with second-generation CYP450 inhibitors or androgen-receptor blockers and untreated or active central nervous system metastases are not allowed; however, prior chemotherapy for hormone-sensitive disease is permitted. Eligible cases will be randomized 1:1 to abiraterone 1000 mg QD + prednisone/prednisolone 5 mg BID plus ipatasertib 400 mg QD or placebo. Crossover between treatment arms is not allowed. Stratification factors are prior taxane-based therapy in the hormone-sensitive setting, progression factor (prostate-specific antigen [PSA] only vs other), presence of liver or lung metastasis, tumor PTEN status by immunohistochemistry (loss vs non-loss) and geographic region. The primary efficacy endpoint is investigator-assessed rPFS (intent-to-treat population and patients with PTEN-loss tumors). Additional endpoints include time to pain progression, time to next cytotoxic chemotherapy, overall survival, additional patient-reported outcomes, time to first opioid use, time to PSA progression, safety and PK. Approximately 850 patients will be enrolled at ~200 centers worldwide.

Clinical trial identification: NCT03072238.

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

Funding: F. Hoffmann-La Roche Ltd

Disclosure: J. de Bono: Scientific advisor: Genentech/Roche Advisory boards: AstraZeneca/MedImmune, Boehringer Ingelheim, GenMab, Glaxo-Smith Kline, Medivation, Merck, Novartis, Pfizer, Sanofi, Vertex, Taiho and Daiichi. S. Bracarda: Advisory Board Member for: Pfizer, Novartis, BMS, Roche, Genentech, MSD, IPSEN, Eusa Pharma, Astellas; Honoraria from: Pfizer, Astellas, Jannsen, Novartis, BMS Travel Reimbursement: Bayer, BMS, Astellas, Jannsen, Ipsen. K. Chi: Adviser and honoraria from Roche/Genetech. C. Massard: Advisory boards, speaker or investigator for: Amgen, Astellas, AstraZeneca, Bayer, Celgene, Genentech, Ipsen, Jansen, Lilly, Novartis, Pfizer, Roche, Sanofi Orion. D. Olmos Hidalgo: Advisory boards for Gentech/Roche (Ipasertib - international - and in local advisory boards of atezolizumab), advisory boards of Janssen, research funding from Janssen. C.N. Sternberg: Research funding to department or consulted: Astellas, Bayer, Janssen, Roche/Genentech, Sanofi, Novartis. S. Gendreau: Employee of Genentech. N. Xu: Employee of Roche and own Roche stocks. T. Baney, D. Maslyar: Employee at Genentech and own stock. C.J. Sweeney: Consultant with compensation: Astellas, Bayer, Genentech, Janssen, Pfizer, Sanofi Research Funding: Astellas, Janssen, Sotio, Sanofi. All other authors have declared no conflicts of interest.

835TiP A phase 2 trial of ODM-201 maintenance therapy in patients with metastatic castration resistant prostate cancer (mCRPC) previously treated with a AR targeting agent and non-progressive on a second line taxane (SAKK 08/16)

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Background: Treatment with the AR targeting agents abiraterone or enzalutamide followed by a taxane is currently the most used treatment for men with mCRPC. Further treatment after response to chemotherapy is only indicated in case of disease progression, with limited treatment options available. ODM-201 (Darolutamide) is a second-generation oral androgen receptor antagonist which has demonstrated a good safety profile and antitumor activity in mCRPC. This trial evaluates whether the immediate use of darolutamide after successful chemotherapy can prolong radiographic progression-free survival (rPFS) compared with watchful waiting in patients with mCRPC.

Trial design: This is a multicenter, randomized, double-blind, placebo-controlled phase 2 trial (NCT02933801) conducted in approximately 19 sites in Switzerland and Italy. Patients with mCRPC are required to have been previously treated with abiraterone or enzalutamide and have no evidence of disease progression on docetaxel or cabazitaxel. Patients (N = 88) will be randomized 1:1 to receive 600 mg darolutamide BID or placebo BID, both with best supportive care, until disease progression. Patients will be stratified by country, WHO performance status (0, 1 vs 2), presence/absence of visceral metastases, enzalutamide vs abiraterone prior to chemotherapy, and planned start of trial treatment after last taxane dose (<35 days vs ≥ 35 days). The primary endpoint is rPFS at 12 weeks after treatment initiation. The secondary endpoints are rPFS, time to PSA progression, time to symptomatic/clinical progression, event-free survival, overall survival, PSA response (30%, 50%, 90%, and best), duration of PSA response (50%), adverse events, and fatigue. The rPFS rate at 12 weeks after treatment initiation will be compared between the two treatment arms using a one-sided test statistic using the Kaplan–Meier method. Recruitment is ongoing, with the first patient randomized on 20.04.2017.

Clinical trial identification: NCT02933801

Legal entity responsible for the study: Swiss Group for Clinical Cancer Research (SAKK)

Funding: Bayer HealthCare Pharmaceuticals Inc.

Disclosure: S. Gillessen: Advisory Boards: AAA International, Active Biotech, Astellas, Bayer, Bristol-Myers Squibb, Curevac, Dendreon Corporation, Ferring, Glaxo Smith Kline, Innocrin Pharmaceuticals, Janssen Cilag, MaxiVAX, Millennium

Pharmaceuticals, Novartis, Pfizer, Orion, Roche, Sanofi Aventis R. Cathomas: Advisory Board for Bayer, Janssen, Astellas, Sanofi, Pfizer, Novartis, Roche, Amgen, AstraZeneca, BMS, MSD. All other authors have declared no conflicts of interest.

836TiP The TRITON clinical trial programme: Evaluation of the PARP inhibitor rucaparib in patients (Pts) with metastatic castration-resistant prostate cancer (mCRPC) associated with homologous recombination deficiency (HRD)

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Background: Recent data show that ≈20% of pts with mCRPC have a germline or somatic alteration in either *BRCA1*, *BRCA2* or *ATM* (homologous recombination [HR] genes) (Robinson et al. *Cell.* 2015;161:1215-28), suggesting these molecular markers may be used to select pts with mCRPC for targeted treatment with a poly(ADP-ribose) polymerase inhibitor (PARPi). PARPis have demonstrated preliminary evidence of antitumour activity in pts with sporadic mCRPC and an HR gene mutation (Mateo et al. *N Engl J Med.* 2015;373:1697-708). These results provide a strong rationale for investigating rucaparib in pts with mCRPC associated with HRD.

Trial design: TRITON2 is a phase 2 study evaluating rucaparib 600 mg BID in pts (n≈160) with mCRPC who have a deleterious germline or somatic *BRCA1*, *BRCA2* or *ATM* mutation (per local and/or central testing). Pts with tumours with an alteration in any of 12 additional prespecified HR genes (eg, *RAD51C*, *RAD51D* or *PALB2*) may enrol in an exploratory cohort. Pts must have progressed on androgen receptor (AR)-targeted therapy and on 1 prior taxane-based chemotherapy for mCRPC. The primary endpoint of TRITON2 is response rate (modified RECIST v1.1/PCWG3 in soft-tissue disease and PSA response with nonmeasurable disease). TRITON3 is a randomised phase 3 study evaluating rucaparib 600 mg BID vs physician's choice of treatment (abiraterone, enzalutamide or docetaxel) in pts (n≈400) with mCRPC with a deleterious germline or somatic *BRCA1*, *BRCA2* or *ATM* mutation (per local and/or central testing). Pts must have progressed on AR-targeted therapy for mCRPC; pts who received prior chemotherapy for mCRPC or PARPi treatment are excluded. Pts will be randomised 2:1 to rucaparib or physician's choice; the latter group may cross over to rucaparib after radiographic progression confirmed by independent radiology review (IRR). The primary endpoint of TRITON3 is IRR-confirmed radiographic progression-free survival (modified RECIST v1.1/PCWG3 criteria). Pretreatment blood samples will be collected from all pts in both trials to enable development of a plasma-based companion diagnostic that predicts rucaparib sensitivity.

Clinical trial identification: TRITON2 – EudraCT 2016-003162-13, NCT02952534; TRITON3 – NCT02975934

Legal entity responsible for the study: Clovis Oncology, Inc.

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837TiP Phase I study of apalutamide (ARN) plus abiraterone acetate (AA), docetaxel (D) in patients (pts) with metastatic castrate-resistant prostate cancer (mCRPC)

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Background: Androgen receptor (AR) targeted therapy is the mainstay of treatment for PC, with potent AR signaling inhibitors and CYP17 inhibitors leading to improved survival. Taxanes are the only chemotherapy class to demonstrate a survival benefit in prospective randomized studies. Docetaxel (D), inhibits AR trafficking from the cytoplasm to the nucleus via stabilizing microtubules, suggesting D may complement AR-pathway targeted therapies. Recent randomized studies showing a > 1 year median survival benefit in men treated with the combination of effective direct AR-targeted therapy combined with D, suggesting that "vertical pathway blockade" in which combinations of AR-directed therapies with complementary mechanisms of action are more effective than sequential use (Sweeney NEJM 2015, James Lancet 2016). Two phase 3 trials are testing the combination of AR signaling inhibitors and CYP17 inhibitors. The safety of combining D with AA is pts with mCRPC was demonstrated in the COU-AA-206 (Tagawa Eur Urol 2016). Combinations of therapies targeting different pathways have the potential to improve efficacy.

Trial design: A multicenter phase 1 dose-escalation study will be conducted to determine the maximum tolerated dose (MTD) of ARN (novel AR signaling inhibitor) combined with AA (CYP17 inhibitor) and D (taxane) in chemotherapy-naïve mCRPC pts with ECOG performance status 0-2. Following determination of MTD, a cohort expansion at the recommended Phase 2 dose will occur. Starting doses are 120 mg/day ARN with 1000 mg/day AA, D 75 mg/m^2 every 3 weeks, and prednisone 5 mg BID. Upon completion of D, pts may continue ARN and AA. The primary endpoint is the safety and tolerability of ARN when dosed with AA and D. Tumor tissue will be collected prospectively to evaluate exploratory biomarkers predictive of response and resistance. In addition, pre- and post-treatment circulating tumor cells will be interrogated for AR localization and AR splice variants. Circulating tumor DNA will also be collected pre- and post-therapy to explore resistance mechanisms.

Clinical trial identification: NCT02913196

Legal entity responsible for the study: Weill Cornell Medical College

Funding: Janssen Scientific Affairs, LLC

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838TiP ARASENS: A phase 3 trial of darolutamide in males with metastatic hormone-sensitive prostate cancer (mHSPC)

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Background: While androgen-deprivation therapy (ADT) demonstrates antitumor activity in mHSPC with prolonged disease control, resistance ultimately occurs and patients die of castration-resistant PC (CRPC). Approximately 10-50% of PC subjects develop CRPC in < 5 yr. Chemohormonal therapy per ESMO guidelines is recommended as first-line treatment of metastatic, castration-naïve disease in men fit enough for chemotherapy. Darolutamide (ODM-201) is a unique investigational oral androgen

receptor (AR) antagonist that binds the AR and AR mutants (eg, W742L and F877L) with high affinity and selectivity, thus, inhibiting receptor function and dihydrotestosterone binding with negligible blood-brain barrier penetration. In the phase 1/2 ARADES and ARAFOR trials, darolutamide had antitumor activity and was well tolerated in men with mCRPC (Fizazi et al. Lancet Oncol 2014; Massard et al. Eur Urol 2016). As a result of this encouraging activity in mCRPC, the ARASENS trial is evaluating darolutamide plus standard ADT + docetaxel in men with mHSPC.

Trial design: This international, randomized, double-blind, placebo-controlled, phase 3 trial (NCT02799602) is being conducted in 23 countries. 1300 men with newly diagnosed mHSPC will be randomized 1:1 to either 600 mg (2 × 300 mg) darolutamide BID with food, equivalent to a total daily dose of 1200 mg or placebo, both with ADT + docetaxel (6 cycles after randomization), and stratified by extent of disease and alkaline phosphatase levels. Key inclusion criteria are confirmed PC with documented metastases, started ADT ± first-generation androgen inhibition therapy ≤12 wk before randomization, and Eastern Cooperative Oncology Group performance status 0 or 1. The primary objective is to show superior overall survival with darolutamide vs placebo, both with ADT + docetaxel. Secondary end points include time to CRPC, initiation of subsequent anticancer therapy, symptomatic skeletal event-free survival (SSE-FS), time to first SSE, initiation of opioid use, pain progression, and worsening of physical symptoms, all measured at 12-wk intervals. Safety will be assessed. The trial is open for enrollment, FPFV was in November 2016, and >110 sites in 16 countries are enrolling.

Clinical trial identification: NCT02799602

Legal entity responsible for the study: Bayer

Funding: Funded by Bayer. Darolutamide was discovered at Orion Corporation and is being jointly developed with Bayer.

Disclosure: M.R. Smith: Consultant for Bayer and Janssen. F. Saad: Consultant, honoraria, research funding from Bayer, Sanofi, Janssen, and Astellas. M. Hussain: Contract to conduct the clinical trial. C.N. Sternberg: Personal fees from Janssen, Sanofi, Astellas, Clovis, Bayer, and Ferring, outside the submitted work. K. Fizazi: Honoraria from Astellas, AstraZeneca, Bayer, Clovis, Curevac, Genentech, Janssen, Orion, and Sanofi. E.D. Crawford: Consultant for Bayer, MDx, Genomic Health, Janssen, Dendreon, and Ferring; honoraria from Bayer and involved in trials with the NIH and University of Colorado Cancer Center; family member employed by Dendreon. K. Yamada: Employee of Bayer US. C. Kappeler: Employee of Bayer AG and own Bayer shares. I. Kuss: Employee of Bayer AG. B. Tombal: Grants and other fees received from Bayer, Astellas, Ferring, and Sanofi; personal fees from Medivation and Janssen.

839TiP A phase II clinical trial of radium-223 activity in patients (pts) with metastatic castration-resistant prostate cancer (mcrpc) with asymptomatic progression while on abiraterone acetate or enzalutamide besides AR-V7 mutational status (EXCAAPE)

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Background: Radium-223 is indicated for pts with mCRPC with symptomatic bone metastases. Biomarkers for radium-223 treatment and its correlation with AR-V7 splice variant, are both under research. The aim of this study is to assess the activity and safety of radium-223 stratified by AR-V7 status in asymptomatic pts who have progressed while on abiraterone acetate or enzalutamide treatment.

Trial design: This is a single-arm, multicenter, phase IIA clinical trial. Pts will receive radium-223 at a dose of 55 kBq per kilogram, given at 4-weeks intervals for 6 intravenous injections, until progression or unacceptable toxicity. We will screen for AR-V7 splice variant and CTCs number after inclusion, at the end of treatment and at progression. We predict that the number of AR-V7[+] pts will be 25% at inclusion. Major inclusion criteria are: (1) mCRPC according to standard Prostate Cancer Working Group (PCWG2)-2 criteria, (2) asymptomatic according to Brief Pain Inventory short form, (3) ≥24 weeks of prior treatment with abiraterone acetate or enzalutamide, (4) adequate organ function and performance status. The primary endpoint is the radiographic progression-free survival (rPFS) according to the PCWG-2 criteria. A total of 52 pts were predefined for the primary analysis using the one arm log-rank test. In both cohorts, we test the null hypothesis that true median rPFS is ≤ 3 months versus the alternative hypothesis that is ≥ 6.3 months. The one-sided type I error was 0.025 in both AR-V7 subgroups. A sample size of 13 pts is needed in the AR-V7[+] subgroup to attain 80% power. In accordance with the expected ratio between cohorts, we will include 39 pts in AR-V7[-] subgroup. The secondary objectives are to investigate the safety of the treatment, to determine the association between AR-V7 status and tumor response and to establish the relationship between circulating tumor cells number with radium-223 activity. Trial registration number is NCT03002220. Date of registration was 20/10/2016. First patient included on 20/12/2016.

Clinical trial identification: NCT03002220, Initial Release Date: 20/Oct/2016

Legal entity responsible for the study: Medica Scientia Innovation Research-MEDSIR

Funding: Bayer Hispania S.L.

Disclosure: M.A. Gonzalez Del Alba Baamonde: Advisory boards Bayer, Astellas, Sanofi, Janssen. Travel expenses: Astellas, Sanofi, Janssen. E. Gallardo Diaz: Advisory boards: Sanofi, Janssen, Astellas, Bayer, Roche, Pfizer. Honoraria: Astellas, Sanofi, Janssen. Travel expenses: Sanofi, Janssen, Astellas, Bayer, Pfizer. Clinical trials: Sanofi, Astellas, Bayer, Bavarian-Nordic, Roche, Pfizer. All other authors have declared no conflicts of interest.

840TiP Stereotactic ablative radiotherapy (SABR) for oligoprogressive metastatic castration-resistant prostate cancer (mCRPC) during abiraterone therapy: A phase I study

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Background: Despite recent therapeutic advances, there is a continuing need for novel prostate cancer treatment strategies. Some men with mCRPC may present at some point with oligometastases, a state between loco-regional and widespread metastatic disease with metastases being limited both in number and location. This oligometastatic state exists de novo, can be induced by effective systemic therapies, or may present under the picture of oligoprogression. The latter is a situation where ≤ 3-5 metastatic tumor sites progress, while all other metastases are controlled by ongoing systemic therapy. The typical practice would be to change systemic therapy at this point. SABR is an emerging treatment option for oligometastatic or oligoprogressive malignancies. Used for this indication SABR may improve survival and delay the need to change systemic therapy. However, some patients may derive limited benefit only because of early and widespread metastatic progression following SABR. While there are no validated biomarkers to predict these two scenarios to date, circulating tumor DNA (ctDNA) is a minimally invasive and highly informative biomarker platform for identifying molecular changes associated with treatment outcome.

Trial design: In the absence of published evidence on the use of SABR for oligoprogressive mCRPC in men undergoing abiraterone therapy, we are conducting a phase I study to determine the incidence of acute and late toxicities (primary endpoint) associated with delivering SABR to all oligoprogressive metastatic sites in 30 men with mCRPC on abiraterone. We also aim to collect preliminary efficacy data of such an approach as secondary endpoints (eg time to biochemical, radiological and/or symptomatic progression following SABR). Using conventional imaging, eligible mCRPC candidates will be identified based on ≤ 5 SABR amenable progressive metastatic lesions (≤ 3 in any one organ system) while all other metastases remain stable or are responding to abiraterone therapy. Before SABR, we will collect ctDNA to perform gene copy number and mutational analyses of prostate cancer relevant genes as a means to predict sustained responses to SABR.

Legal entity responsible for the study: Sunnybrook Research Institute, Toronto, ON, Canada

Funding: Janssen Inc., Canada

Disclosure: U. Emmenegger: Research support for this study and paid advisory board meetings of the manufacturer of abiraterone. All other authors have declared no conflicts of interest.

841TiP A randomized phase II study comparing cabazitaxel/prednisone to cabazitaxel alone for second-line chemotherapy in men with metastatic castrate resistant prostate cancer (mCRPC): CABACARE

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Background: In theTROPIC study, cabazitaxel (CAB), administered with prednisone (PDN) 10 mg daily, showed significant advantage in OS and PFS in patients (pts) progressing during or after docetaxel (DOC) treatment. Similar to DOC, CAB has been approved in combination with daily PDN, although the contributing role of PDN to

efficacy and safety has been poorly investigated. Corticosteroids have a variety of effects, which may be either favourable, mediated by adrenal androgen and cytokine suppression, or detrimental, because of adverse events associated with long-term use, promiscuous activation of AR, immunosuppression, activation of AR variants highly sensitive to PDN even at low concentrations. Moreover PDN acts as a CYP3A4 inducer, affecting clearance of taxanes. It has been shown that AR point mutations are rare in therapy-naive pts but occur in 15-45% of CRPC pts and can increase AR affinity for a wide range of steroids. Over 100 mutations have been described. In the CHAARTED trial DOC was safely administered without daily PDN showing important clinical benefits in OS, PFS, and time to CRPC.; Safety data for CAB without PDN are lacking. AR-V7 positivity and RB loss/inactivation have been identified as potentially implicated in progression with next-generation targeted agents. We also would like to prospectively assess their role as predictive biomarkers of CAB activity.

Trial design: CABACARE is a randomized, phase II, open label, multicenter study comparing CAB at 25 mg/m2 q21 plus daily PDN (10 mg) vs CAB at 25 mg/m2 q21 alone in mCRPC pts progressed during or after DOC treatment. The study is designed to test non-inferiority in terms of PFS, according to PCWG-2, of CAB alone vs CAB plus PDN, assuming that the two arms are equally effective. Each arm will enroll 110 pts. Main secondary objectives are: safety, QoL, pain assessment, overall response rate (ORR), PSA response, time to PSA progression, time to radiological progression; OS; and time to skeletal related events (SRE). The influence of Arv7 and RB status on CAB activity will also be evaluated

Clinical trial identification: EUDRACT 2016- 005251-25

Legal entity responsible for the study: Consorzio Oncotech

Funding: Sanofi-Aventis

Disclosure: C. Buonerba: Consultant for Sanofi. Research support to institution from Sanofi, Astellas, Quercegen Pharmaceuticals. Travel expenses from Janssen-Cilag. S. De Placido: Research Support to Institution from Sanofi, Astellas, Quercegen Pharmaceuticals. G. Di Lorenzo: Consultant for Sanofi. Research Support to Institution from Sanofi, Astellas, Quercegen Pharmaceuticals.

842TiP PROSABI: Prospective multi-centre study of prognostic factors in castration resistant prostate cancer (CRPC) patients treated with abiraterone acetate (AA)

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Background: The evolution of CRPC is heterogeneous, and despite progress in its management, with several new agents approved for CRPC, we are still so far from being able to predict which group of patients might benefit from a particular strategy. Therefore, the identification of new predictive and prognostic biomarkers is urgently needed.

Trial design: PROSABI is a prospective multicentre observational study in metastatic CRPC designed to explore biomarkers in patients treated with AA. Key inclusion criteria: a) histological confirmation of prostate cancer; b) documented criteria (PCWG2) for CRPC; c) availability of tumour tissue; d) candidate for standard treatment with AA. Primary end point: to validate the prognostic value for overall survival (OS) of the expression signature (ES) in peripheral blood of 9 genes described by Olmos et al (Lancet Oncol 2012). Secondary end points: a) to study the prognostic role for progression-free survival of the ES; b) to analyse the prognostic role for OS of early changes in the ES; c) to compare the prognostic and predictive utility of the ES with other ES (Ross et al, Lancet Oncol 2012); d) to validate in this patient cohort prognostic nomograms described for CRPC. Exploratory outcomes: a) to establish prognostic value for TMPRSS-ERG and PTEN; b) to determine the prognostic value for serum testosterone levels; c) to analyse the role of serum chromogranine; d) to study the prognostic role of AR splicing variants; e) to explore new somatic and germinal variants in peripheral blood and tissue associated to dissemination, response and resistance to AA. PROSABI is part of the PROCURE Biomarkers network, a multicentric spanish platform for biomarkers discovery in CRPC patients. 220 patients will be accrued to provide appropriate statistical power to detect at least 91 events (deaths) to analyse the main outcome. Currently, 48 centres are active for recruitment and 184 patients have been included. Blood samples are collected before, during (pre-cycle 3) and after progression to AA. Prospective data collection will be linked. This study may help to incorporate new biomarkers in clinical practice and improve the selection of therapy in mCRPC.

Clinical trial identification: NCT02787837

Legal entity responsible for the study: Spanish National Cancer Research Centre (CNIO)

Funding: Spanish National Cancer Research Centre + grant from Janssen

Disclosure: All authors have declared no conflicts of interest.

843TiP PRORADIUM: Prospective multicentre study of prognostic factors in castration resistant prostate cancer (CRPC) patients treated with radium-223

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Background: Several new agents have been approved for CRPC, but we are still so far from being able to predict which group of patients might benefit from a particular strategy. Therefore, the identification of new predictive and prognostic biomarkers is urgently needed. In this setting, bone metabolism markers (BMM) assume particular importance regarding to R223.

Trial design: PRORADIUM is a prospective multicentre observational study in metastatic CRPC designed to explore biomarkers in patients treated with R223. Key inclusion criteria: a) histological confirmation of prostate cancer; b) documented criteria (PCWG2) for CRPC; c) availability of tumour tissue; d) candidate for standard treatment with R223. Primary end point: to validate the prognostic value for overall survival (OS) of serum BMM expression described by Primo N Lara et al (JNCI 2014). Secondary end points: a) to analyse the prognostic role for PSA response regarding to BMM expression; b) to correlate radiological response with BMM; c) to investigate the association of skeletal related events with BMM; d) to analyse the prognostic role of

alkaline phosphatase before and during R223; e) to analyse the prognostic value of "Bone Scan Index" in response evaluation; f) to analyse the prognostic role for OS of AR-V7 and AR amplification; g) to validate the prognostic role of the expression signature described by Olmos et al (Lancet Oncol 2012) in peripheral blood. Exploratory outcomes: a) to validate prognostic nomograms described for CRPC; b) to explore new somatic and germinal variants in peripheral blood and tissue associated to response and resistance to R223. PRORADIUM is part of the PROCURE Biomarkers network, a multicentric spanish platform for biomarkers discovery in CRPC patients. 161 patients will be accrued to provide appropriate statistical power to detect at least 85 events (deaths) to analyse the main outcome. Currently, 48 centres are active for recruitment and 54 patients have been included. Blood samples are collected before, during and after progression to R223. Prospective data collection will be linked. This study may help to incorporate new biomarkers in clinical practice and improve the selection of therapy in mCRPC.

Clinical trial identification: NCT02925702

Legal entity responsible for the study: Spanish National Cancer Research Centre (CNIO)

Funding: Bayer Hispania, S.L

Disclosure: A. Medina: Honoraria from Bayer Hispania, S.L. All other authors have declared no conflicts of interest.

844TiP PROSENZA: Prospective multi-centre study of prognostic factors in castration resistant prostate cancer (CRPC) patients treated with enzalutamide (ENZ)

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Background: CRPC is a heterogeneous disease, and despite new agents approved, the optimal sequence of treatment remains unclear, far from personalised medicine that may offer the maximal benefit for the patient. For that reason, our aim is the identification of new biomarkers in CRPC patients treated with conventional therapy.

Trial design: PROSENZA is a prospective multicentre observational study in metastatic CRPC designed to explore biomarkers in patients treated with ENZ. Key inclusion criteria: a) histological confirmation of prostate cancer; b) documented criteria (PCWG2) for CRPC; c) availability of tumour tissue; d) candidate for standard treatment with ENZ. Primary end point: to study the prognostic value for overall survival (OS) of the detection of androgen receptor splicing variant 7 (AR-V7) and/or amplification of AR (AR+) in peripheral blood in this cohort. Secondary end points: a) to analyse the correlation between PSA response and AR-V7 and/or AR+; b) to evaluate the correlation between radiological response and AR-V7 and/or AR+; c) to study changes in AR-V7 frequency and/or AR+ pre and post ENZ; d) to analyse and correlate the prognostic role of AR-V7 and AR+ with other biomarkers as testosterone serum levels, PTENloss or TMPRSS-ERG fusions. Exploratory outcomes: a) to validate in this cohort prognostic nomograms described for CRPC; b) to validate the prognostic role of the expression signature described by Olmos et al (Lancet Oncol 2012) in peripheral blood; c)to explore new somatic and germinal variants in peripheral blood and tissue associated to dissemination, response and resistance to ENZ. PROSENZA is part of the PROCURE Biomarkers network, a multicentric spanish platform for biomarkers discovery in CRPC. 187 patients will be accrued to provide appropriate statistical power to detect at least 71 events (deaths) to analyse the main outcome. Currently, 48 centres are active for recruitment and 54 patients have been included. Blood samples are collected before, during and after progression to ENZ Prospective data collection will be linked. This study may help to incorporate new biomarkers in clinical practice and improve the selection of therapy in mCRPC.

Clinical trial identification: NCT02922218

Legal entity responsible for the study: Spanish National Cancer Research Centre

Funding: Partially funded by Astellas

Disclosure: A. Medina: Honoraria from Astellas. All other authors have declared no conflicts of interest.

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GENITOURINARY TUMOURS, NON-PROSTATE

845O Phase III randomized, sequential, open-label study to evaluate the efficacy and safety of sorafenib-pazopanib versus pazopanib-sorafenib in the treatment of metastatic renal cell carcinoma (SWITCH-II)

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Background: The previous SWITCH-I study explored the two possible sequences of Sunitinib and Sorafenib for the treatment of advanced/metastatic renal cell carcinoma (mRCC) and showed similar total progression-free-survival (tPFS) and overall survival (OS) times. This trial compared the sequential therapy with the multikinase inhibitors Sorafenib (So) followed by Pazopanib (Pa) or vice versa in mRCC patients (pts).

Methods: This multicentre, randomised phase 3 study assessed the sequential use of So-Pa versus Pa-So in pts with mRCC without prior systemic therapy. Pts were randomised to So 400 mg twice daily followed by Pa 800 mg once daily (So-Pa) in case of progression or intolerable toxicity or vice versa (Pa-So). The primary endpoint was non-inferiority of tPFS with So−Pa compared to Pa−So, assessed from randomisation to progression or death during second-line therapy defined as hazard ratio (HR) <1.225 as a one-sided 95% confidence interval (CI). Main secondary endpoints included OS, total time to progression (TTP), disease control rate (DCR), 1st-line and 2nd-line PFS as well as safety and tolerability.

Results: 377 pts were randomised (So-Pa, n = 189; Pa-So, n = 188). Median tPFS was 8.6 mo (95% CI 7.7-10.2) for So-Pa and 12.9 mo (95% CI 10.8-15.2) for Pa-So with a HR of 1.36 (upper limit of one-sided 95% CI 1.68). Therefore, non-inferiority of So-Pa in regard to tPFS was not met. However, marked statistical differences were noted in favour of Pa-So in total TTP, 1st-line PFS and DCR but not for OS and 2nd-line PFS. In the So-Pa arm 106/189 (56%) received Pa as 2nd line and for the Pa-So arm 87/188 (46%) received So as 2nd line. The most frequent any-grade treatment-emergent first-line adverse events for So were diarrhoea (56%), fatigue (37%) and hand-foot skin reaction (35%) and for Pa diarrhoea (60%), hypertension (48%) and fatigue (45%).

Conclusions: Non-inferiority of the sequence So-Pa compared to Pa–So in terms of the primary endpoint tPFS was not met. However, superiority of the sequence Pa-So over So-Pa for tPFS was not proven either, since the study design was computed with a HR of < 1.225 as a one-sided 95% CI.

Clinical trial identification: NCT01613846, first received May 4, 2012

Legal entity responsible for the study: Technische Universität München

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Disclosure: M. Retz: Honoraria Advisory boards and lectures: Bristol-Myers Squib, Janssen-Cilag, Roche, MSD, Ipsen, Merck-Pfizer, Novartis, Bayer. J. Bedke: Consultancies, honoraria or study participation from Bayer, Bristol-Myers Squib, GSK, Immatics, Nektar, Novartis, Pfizer and Roche. M-O. Grimm: Consultancy fees: AstraZeneca, Amgen, Bayer Health Care, Bristol-Myers Squib, GSK, Novartis, Pfizer, Sanofi; grants: Novartis, Bristol-Myers Squib; payment for lectures: Bayer Health Care, Bristol-Myers Squib, GSK, Hexal, Janssen Cilag, JenaPharm, Novartis, Pfizer, Pierre Fabre. M. De Santis: Study Grants: Pierre Fabre; Honoraria: Amgen, Astellas, AstraZeneca, Bayer, Bristol-Myers Squib, Celgene, Dendreon, Eisai, ESSA, Ferring, GSK, Ipsen, Janssen, Merck, MSD, Novartis, Pfizer, Pierre Fabre, Roche, Sanofi, SeaGen, Shionogi, Synthon, Takeda, TevaOncoGenex. J.E. Gschwend: Honoraria Advisory boards and lectures: Amgen, Astellas, Bayer, Eisai, Janssen, Novartis, Pierre-Fabre, Roche. All other authors have declared no conflicts of interest.

846O Final results of a phase I study of cabozantinib (cabo) plus nivolumab (nivo) and cabonivo plus ipilimumab (Ipi) in patients (pts) with metastatic urothelial carcinoma (mUC) and other genitourinary (GU) malignancies

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Background: We report the updated safety and efficacy of CaboNivo and CaboNivoIpi in pts with mUC and other GU tumors (NCT02496208).

Methods: Primary objective was to determine the dose limiting toxicity (DLT) and recommended phase 2 dose (RP2D). We tested 7 dose levels (DL); 4 in part 1 (CaboNivo); 3 in part 2 (CaboNivoIpi). **Part 1** pts received cabo PO daily/Nivo IV q2wks: **DL1** Cabo 40mg/Nivo 1mg/kg, **DL2** Cabo 40mg/Nivo 3mg/kg, **DL3** Cabo 60mg/Nivo1mg/kg, **DL4** Cabo 60mg/Nivo 3mg/kg. **Part 2** pts received Cabo PO daily/Nivo/Ipi IV q3wks x4 cycles → Nivo IV q2wks: **DL5** Cabo 40mg/Nivo1&Ipi 1mg/kg, **DL6** Cabo 40mg/Nivo 3&Ipi 1mg/kg, **DL7** Cabo 60mg/Nivo3&Ipi 1mg/kg. Adverse events (AEs) were graded by CTCAE v4.0. Other objectives: overall response rate (ORR), duration of response (DOR), progression-free survival (PFS) and overall survival (OS).

Results: From 07/15/2015-04/25/2017, median(m) potential follow-up: 13.4 month-s(mo). 42 pts enrolled: 24 pts in **part 1** (mUC n = 7; urachal (Ur) n = 4; germ cell tumor n = 4; prostate cancer (PC) n = 4; bladder squamous cell carcinoma (bSCC) n = 2; penile n = 1; sarcomatoid renal cell carcinoma (sRCC) n = 1; and trophoblastic n = 1); 18 pts in **part 2** (mUC n = 8; penile n = 3; CRPC n = 5; sertoli n = 1; sRCC n = 1). Median age: 56 years (range 31-77), 90.5% male. Grade 3–4 AEs occurred in 67% of pts, mostly in **part 1:** hypophosphatemia (21%), neutropenia (21%), fatigue (12%), elevated lipase (12%); diarrhea, hypertension (HTN), dehydration, thrombocytopenia, proteinuria, and leukopenia (8% each); in **part 2:** hypophosphatemia (22%) HTN (17%); fatigue, nausea, lymphopenia, and elevated lipase (11% each). G3 immune-related AEs: aseptic meningitis (n = 1, DL1) and colitis (n = 1, DL5). No G5 toxicities or DLTs. RP2D for **part 1**: Cabo40mg/Nivo3mg/kg; for **part 2**: Cabo40mg/Nivo3&Ipi1mg/Kg. ORR=35%, 3CR (2mUC, 1SCC) & 11PR (3mUC, 2SCC, 2sRCC, 2Penile, 1Ur, 1PC). mDOR (CR+PR+SD): 7.1 mo [95% CI: 5.1-not reached], mPFS: 5.5 mo [95%CI: 4.5-12.8] and mOS was not reached. OS at 6&12 mo was 83.3%&64.3%.

Conclusions: CaboNivo and CaboNivoIpi showed durable clinical activity in mUC and rare GU malignancies with manageable toxicity.

Clinical trial identification: Trial Protocol Number: NCT02496208, release date: 07/15/2015

Legal entity responsible for the study: National Cancer Institute, National Health Institutes.

Funding: Cancer Therapy Evaluation Program

Disclosure: All authors have declared no conflicts of interest.

847O A phase 1b/2 trial of lenvatinib plus pembrolizumab in patients with renal cell carcinoma

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Background: Lenvatinib (LEN) is a multikinase inhibitor of vascular endothelial growth factor (VEGF) receptor 1 − 3, fibroblast growth factor receptor 1 − 4, platelet-derived growth factor receptor α, RET, and KIT. LEN was approved in combination with everolimus to treat advanced renal cell carcinoma (RCC) after 1 prior VEGF-targeted treatment. We report results for the RCC cohort of a phase 1b/2 trial of LEN+pembrolizumab (pembro) in patients (pts) with selected solid tumors (NCT02501096).

Methods: This was a multicenter open-label study. Pts had metastatic clear cell RCC, measurable disease according to immune-related Response Evaluation Criteria in Solid Tumors (irRECIST), and Eastern Cooperative Oncology Group performance status ≤1. LEN 20 mg/d plus pembro 200 mg intravenously every 3 weeks was assessed as the maximum tolerated dose and recommended phase 2 dose in phase 1b. Tumor

assessments were performed by trial investigators using irRECIST. The primary phase 2 endpoint was objective response rate (ORR) at 24 weeks. Secondary endpoints included ORR, progression-free survival (PFS), and duration of response (DOR).

Results: 30 Pts were enrolled in either the phase 1b (8 pts) or phase 2 cohort (22 pts). Data cutoff Feb 15, 2017. 11 (37%) Pts had 0, 11 (37%) pts had 1, and 8 (27%) pts had ≥2 prior anti-cancer therapies. Of pts who received prior medication (n = 19, 63%), 16 (53%) received prior VEGF-targeted therapy. Efficacy outcomes are summarized in the Table. At data cutoff, 17 (57%) pts were still receiving treatment, 8 (27%) completed treatment due to disease progression, and 5 (17%) discontinued treatment. The most common any-grade treatment-emergent adverse events were diarrhea, fatigue, hypothyroidism, nausea, and stomatitis. Toxicities were manageable with dose interruption and/or modification and no new safety signals were found. Updated data will be presented.

Table: 847O

Outcome	n = 30	95% CI
ORR, n (%)	19 (63.3)	43.9%–80.1%
Median PFS, mos	NE	9.9–NE
Median DOR, mos	NE	8.4–NE

NE, not estimable.

Conclusions: Combination treatment with LEN+pembro showed promising antitumor activity and an acceptable safety profile. A phase 3 trial of LEN+pembro and LEN+everolimus, vs sunitinib in first-line treatment for metastatic clear cell RCC is ongoing.

Clinical trial identification: NCT02501096

Legal entity responsible for the study: Eisai Inc

Funding: Eisai Inc

Disclosure: C-H. Lee: Research funds to institute from Eisai, Bristol-Myers Squib, Pfizer, Exelixis, Calithera, and consulting fees from Exelixis. D. Rasco: Research funding from Aeglea, Asana, Ascentage, Bayer, Celgene, Eisai, Five Prime Therapeutics, GlaxoSmithkline, Macrogenics, Merck, Millennium Pharmaceuticals, OncoMed Pharmaceuticals, Pharmacyclics, Rexahn Pharmaceuticals, Santa Maria Biotherapeutics. M. Taylor: Honoraria from/held consulting advisory role with: Eisai, Bristol-Myers Squib, Blueprint Medicine, and Trillium Pharma; participated in speakers' bureau for Eisai Inc. C. Dutcus, R. Shumaker, D. Stepan, D. Li: Employee of Eisai Inc. E.V. Schmidt: Employee of/stockholder: Merck Research Labs. R.J. Motzer: Grants from Pfizer, Eisai, Exelixis, Novartis, and Bristol-Myers Squib. Served as a consultant to Pfizer, Eisai, Exelixis, and Novartis. All other authors have declared no conflicts of interest.

848PD Impact of zumor mutation burden on nivolumab efficacy in second-line urothelial carcinoma patients: Exploratory analysis of the phase ii checkmate 275 study

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Background: Nivolumab, a programmed death (PD)-1 inhibitor, demonstrated efficacy in a single-arm phase II study in patients (pts) with metastatic or surgically unresectable urothelial carcinoma (UC) (CheckMate 275; Sharma et al. 2017). The current analysis explores the potential association between pretreatment tumor mutation burden (TMB) and response to nivolumab.

Methods: Tumor DNA from pretreatment archival tumor tissue and matched whole blood samples was profiled by whole exome sequencing. TMB was defined as the total number of missense somatic mutations per tumor, and was evaluated as a continuous variable and by tertiles (missense count: high ≥167, medium 85–166, low <85). Cox models were used to explore the association between TMB and progression-free survival (PFS) and overall survival (OS); and logistic regression for objective response rate (ORR). Tumor PD-ligand 1 (PD-L1) expression was assessed by Dako PD-L1 immunohistochemistry 28-8 assay and was categorized as </≥1%.

Results: 139 (51%) of 270 pts had evaluable TMB. Baseline characteristics, ORR, PFS, and OS were similar between all treated pts and the TMB subgroup. ORR, PFS and OS in all pts and TMB/PD-L1 subgroups are shown in the Table. TMB showed a statistically significant positive association with ORR (P=0.002) and PFS (P=0.005), and a strong association with OS (P=0.067), even when adjusted for baseline tumor PD-L1 expression, liver metastasis status, and serum hemoglobin. High TMB had the greatest impact on survival in pts with <1% PD-L1 expression (Table).

Conclusions: These exploratory findings suggest that TMB may enrich for response to nivolumab and may provide complementary prognostic/predictive information beyond PD-L1. Further analyses in randomized trials are warranted to define the prognostic/predictive value of TMB in the context of other biomarkers in UC pts treated with immunotherapy.

Clinical trial identification: NCT02387996

Legal entity responsible for the study: Bristol-Myers Squibb

Funding: Bristol-Myers Squibb

Disclosure: M.D. Galsky: Received research funding from Bristol-Myers Squib, Novartis, and Merck and has served on advisory boards for Genentech, Merck, EMD-Serono, and AstraZeneca. A. Saci: Reports being an employee of Bristol-Myers Squibb during the conduct of the study. A. Azrilevich: Reports being an employee of the sponsor, Bristol-Myers Squibb. C. Horak: Reports being an employee and stockholder of Bristol-Myers Squibb A. Lambert: Reports employment and stock owner from Bristol-

Table: 848PD ORR, PFS and OS: All patients and TMB/PD-L1 subgroups

	All pts N = 270		TMB subgroup N = 139		TMB high N = 47		TMB medium N = 46		TMB low N = 46	
ORR, %	20.0		20.1		31.9		17.4		10.9	
PFS, months median	2.00		2.00		3.02		1.87		1.91	
(95% CI)	(1.87–2.63)		(1.87–3.02)		(1.87–NR)		(1.68–3.65)		(1.84–3.15)	
OS, months median	8.57		7.23		11.63		9.66		5.72	
(95% CI)	(6.05–11.27)		(5.72–11.63)		(5.82–NR)		(4.76–NR)		(4.21–11.30)	
	PD-L1 <1% N = 146	PD-L1 ≥1% N = 124	PD-L1 <1% N = 69	PD-L1 ≥1% N = 70	PD-L1 <1% N = 23	PD-L1 ≥1% N = 24	PD-L1 <1% N = 21	PD-L1 ≥1% N = 25	PD-L1 <1% N = 25	PD-L1 ≥1% N = 21
ORR, %	15.8	25.0	17.4	22.9	30.4	33.3	23.8	12.0	0	23.8
PFS, months median	1.87	3.53	1.87	2.30	3.02	3.52	1.77	1.94	1.77	3.12
(95% CI)	(1.77–2.04)	(1.94–3.71)	(1.71–3.02)	(1.87–3.71)	(1.81–NR)	(1.87–NR)	(1.54–5.78)	(1.68–3.71)	(1.68–2.10)	(1.87–7.23)
OS, months median	5.95	11.63	5.68	10.28	NR	10.60	4.53	11.30	4.96	8.57
(95% CI)	(4.37–8.08)	(9.10–NR)	(4.40–NR)	(6.05–NR)	(4.70–NR)	(5.82–NR)	(2.23–NR)	(5.85–NR)	(2.92–NR)	(4.21–NR)

ORR based on blinded independent review committee assessment CI = confidence interval; NR = not reached

Myers Squibb, outside the submitted work. A. Siefker-Radtke: Reports being on the Scientific advisory board for AstraZeneca, Bristol-Myers Squibb, Eisai, EMD Serono, Genentech, Inovio, Janssen, and Merck, outside the submitted work. A. Necchi: Reports consulting or advisory role from AstraZeneca, Bayer, Roche, Merck & Co. Inc., and Pfizer; Reports research funding from Amgen, AstraZeneca, and Merck & Co. Inc., outside the submitted work. P. Sharma: Reports being a consultant for Bristol-Myers Squibb, Glaxo Smith Kline, AstraZeneca, Amgen, Constellation, Jounce, Kite Pharma, Neon, Evelo, EMD Sereno, Astellas; stock from Jounce, Kite Pharma, Evelo, Constellation, Neon, outside the submitted work. All other authors have declared no conflicts of interest.

849PD Comparison of tumor mutational burden (TMB) in relevant molecular subsets of metastatic urothelial cancer (MUC)

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Background: Phase I and II studies suggest potential benefit with targeted therapy (TT) (e.g., FGFR3, ERBB2/3 and CDK4/6 inhibitors) in relevant molecular subsets of MUC. Given increasing data supporting PD-1/PD-L1 inhibitors in MUC, rationale for combinations of TT and immunotherapy (IO) is sought. TMB is a putative biomarker of IO response; we investigated differences in TMB in relevant molecular subsets of MUC.

Methods: DNA was extracted from 40 microns of FFPE sections from 2024 consecutive patients with MUC. Comprehensive genomic profiling (CGP) was performed on hybridization-captured, adaptor ligation based libraries to a mean coverage depth of 688X for up to 315 cancer-related genes plus 37 introns from 14 genes frequently rearranged in cancer. The CGP assay included base substitutions (SUB), INDELs, copy number alterations (CNA) and fusions/rearrangements. TMB was determined on 1.2 million Mb of sequenced DNA; results are reported for the overall cohort and in subsets segregated separately by presence or absence of FGFR3, ERBB2/3, PIK3CA and CDKN2A/B alteration.

Results: 2024 consecutive pts (1457:567 M:F) with MUC were assessed with a median age of 67 years. Median TMB in the overall cohort was 7.2 mutations/Mb. *FGFR3, ERBB2, ERBB3, PIK3CA,* and *CDKN2A/B* alteration were identified in 23%, 14%, 4%, 19% and 37% of pts, respectively. TMB was significantly different in pts segregated based on *ERBB2* alteration ($P = 1.8\text{x}10^{-7}$), *PIK3CA* alteration ($P = 1.7\text{x}10^{-6}$) and *ERBB3* mutation ($P = 0.01$) (Table). *ERBB2* and *FGFR3* genomic alterations (GAs) were significantly mutually exclusive, while *FGFR3* GAs significantly co-occurred with *PIK3CA* and *CDKN2A/B*. Further differences in CGP amongst these subsets will be presented at the meeting.

Table: 849PD

	TMB, muts/Mb Median (IQR 25%-75%)
All patients (n = 2024)	7.2 (3.6, 11.7)
FGFR3 alteration	
Yes (n = 461)	6.3 (3.8, 10.8)
No (n = 1564)	7.2 (3.6, 12.6)
ERBB2 alteration	
Yes (n = 277)	9.9 (5.4, 18.0)
No (n = 1747)	6.3 (3.6, 11.3)
ERBB3 alteration	
Yes (n = 72)	10.8 (6.3, 20.3)
No (n = 1952)	6.3 (3.6, 11.7)
PIK3CA alteration	
Yes (n = 383)	9.0 (4.8, 17.1)
No (n = 1641)	6.3 (3.6, 10.8)
CDKN2A/B alteration	
Yes (n = 742)	7.2 (3.6, 12.6)
No (n = 1282)	6.3 (3.8, 11.3)

Conclusions: Given the proposed correlation between TMB and IO response, these data may inform the utility of combination strategies. Specifically, given higher TMB in pts with ERBB2/ERBB3 or PIK3CA alteration, combination studies exploring IO with TT directed at these targets may be warranted.

Legal entity responsible for the study: Sumanta K. Pal, MD

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850PD Epithelial-mesenchymal transition (EMT), T cell infiltration, and outcomes with nivolumab (nivo) in urothelial cancer (UC)

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Background: The presence of tumor infiltrating lymphocytes has been associated with a higher objective response rate (ORR) to PD-1/PD-L1 blockade. Across a variety of cancers, high EMT gene expression correlates with increased T cell infiltration. The impact of these interrelated processes on outcomes with PD-1/PD-L1 blockade has not been defined.

Methods: The TCGA UC cohort (n = 405) was utilized to determine the relationship between EMT gene signature (sig) expression (200 genes in MSigDB) and infiltrating T cell abundance (ITA). ITA was inferred using mRNA expression of 144 T cell genes. A phase 2 trial of nivo in metastatic UC (CheckMate 275, n = 212) was used to determine the impact of EMT sig (HTG EdgeSeq) and CD8 expression (IHC) on ORR, progression-free (PFS), and overall survival (OS).

Results: In the TCGA cohort, EMT sig correlated with ITA (CC = 0.60, $p < 2e\text{-}16$). The correlation remained significant after correction for sample purity (CC = 0.37, p = 1e-14) and UC molecular subtype (p = 1e-13). In the CheckMate 275 cohort, EMT sig correlated with CD8 expression (CC = 0.29, p = 2e-05). The impact of EMT sig and CD8 expression on outcomes is shown (Table). Higher CD8 expression was associated with longer PFS (p = 0.0003) and OS (p = 0.01). There was a significant interaction between EMT sig and CD8 (PFS, p = 0.038; OS, p = 0.064); in $CD8_{high}$ tumors, ORR, PFS, and OS were worse in EMT_{high} vs EMT_{low}.

Table: 850PD Outcomes with nivolumab

Group	N	ORR	Median PFS (95% CI)	Median OS (95% CI)
Entire cohort	212	18.4%	1.97 (1.87-2.46)	8.74 (5.58-NR)
$CD8_{low}$	106	11.3%	1.84 (1.71-1.94)	5.72 (4.3-8.74)
$CD8_{high}$	106	25.5%	3.12 (2.04-4.14)	11.30 (10.9-NR)
EMT_{low}	106	23.6%	2.10 (1.87-3.65)	8.74 (6.05-NR)
EMT_{high}	106	13.2%	1.91 (1.81-2.46)	6.57 (4.96-NR)
$CD8_{high}$ EMT_{high}	64	15.6%	2.04 (1.84-3.52)	NR (6.57-NR)
$CD8_{high}$ EMT_{low}	42	40.5%	5.52 (3.45-NR)	NR (11.3-NR)

Conclusions: While much effort has been focused on "turning cold tumors hot" as a strategy to improve the efficacy of PD-1/PD-L1 blockade, a large proportion of "hot tumors" do not respond. Among "hot" UC, EMT_{high} tumors are associated with a lower ORR to nivo and shorter PFS and OS. These findings substantiate EMT as a potential mechanism of immune escape and raise the possibility of co-targeting EMT and PD-1/PD-L1 in "hot" UC.

Clinical trial identification: NCT02387996

Legal entity responsible for the study: Matthew Galsky

Funding: Bristol-Myers Squib

Disclosure: M.D. Galsky: Received research funding from Bristol-Myers Squib, Novartis, and Merck and has served on advisory boards for Genentech, Merck, EMD-Serono and AstraZeneca. A. Saci and P.M. Szabo: Employees of Bristol-Myers Squib. All other authors have declared no conflicts of interest.

851PD Subgroup analyses from KEYNOTE-045: Pembrolizumab (pembro) versus individual investigator's choice of chemotherapy (paclitaxel, docetaxel, or vinflunine) in recurrent, advanced urothelial cancer (uc)

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Background: In the open-label, phase 3 KEYNOTE-045 study (NCT02256436), overall survival (OS) was significantly longer with pembro vs investigator's choice of chemo (median, 10.3 vs 7.4 mo; hazard ratio [HR], 0.73; P = 0.002) in recurrent, advanced UC. In a post hoc analysis, pembro was compared with the individual agents in the chemo arm.

Methods: Pts with histologically or cytologically confirmed UC, progression after platinum, ECOG PS 0-2, measurable disease (RECIST v1.1), and ≤2 lines of systemic therapy were randomly assigned 1:1 to pembro 200 mg Q3W or investigator's choice of paclitaxel 175 mg/m^2 Q3W, docetaxel 75 mg/m^2 Q3W, or vinflunine 320 mg/m^2 Q3W. Primary end points: OS and PFS (RECIST v1.1, blinded central review). ORR (RECIST v1.1, blinded central review) was a secondary end point.

Results: 525 pts were included in these analyses (allocation: pembro, 270; paclitaxel, 84; docetaxel, 84; vinflunine, 87). Baseline demographics were generally balanced among the 4 groups. Median follow-up was 14 mo (range, 10-22 mo). Pembro was associated with an OS benefit over the individual chemo agents (HR [95% CI]: paclitaxel, 0.77 [0.57-1.06]; docetaxel, 0.78 [0.56-1.08]; vinflunine, 0.71 [0.52-0.96]). PFS was similar between pembro and each of the chemo agents. ORR (95% CI) was 21% (16%-27%) with pembro vs 12% (6%-21%), 6% (2%-13%), and 18% (11%-28%) with paclitaxel, docetaxel, and vinflunine, respectively. Treatment-related AEs occurred in 61% (pembro), 88% (paclitaxel), 92% (docetaxel), and 91% (vinflunine) of pts. 15% (pembro), 44% (paclitaxel), 54% (docetaxel), and 51% (vinflunine) experienced treatment-related AEs of grade ≥3 severity.

Conclusions: Results from subgroup analyses of KEYNOTE-045 demonstrate that pembro was associated with longer OS, higher antitumor activity, and lower incidence of toxicities than single-agent paclitaxel, docetaxel, or vinflunine in pts with advanced UC that progressed on/after platinum-based therapy. Pembro is the first agent to demonstrate OS improvement vs chemo in this setting and should be considered for use in recurrent, advanced UC.

Clinical trial identification: NCT02256436; September 29, 2014

Legal entity responsible for the study: Merck & Co., Inc.

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852PD Atezolizumab (atezo) in platinum-treated locally advanced or metastatic urothelial carcinoma (mUC): Post-progression outcomes from the phase 2 IMvigor210 study

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Background: mUC remains a disease with few treatment (tx) options and short OS. IMvigor210 demonstrated efficacy and safety of atezo (anti–PD-L1) in mUC and led to approval in the US and elsewhere. Here, we evaluate outcomes in platinum-treated IMvigor210 patients (pts) treated with atezo beyond progression.

Methods: IMvigor210 (NCT02108652 cohort 2) enrolled pts with mUC that progressed during/following platinum. Atezo was given 1200 mg IV q3w until loss of clinical benefit per investigator. In this descriptive, post hoc analysis (data cut 4 Jul 2016), assessments included on-study RECIST v1.1 response (pre– and post–first progressive disease [PD]; central review), sum of target lesion diameters (SLD; % change from PD), OS, post-progression (pp) OS and safety grouped by tx status post-PD.

Results: 220 pts who experienced PD (of 310 total in study) were evaluable: 137 continued atezo post-PD, and 83 received other (n = 19) or no (n = 64) systemic tx. Pts who continued atezo had fewer poor prognostic factors (Table). Pre-PD tx duration was similar in pts who did or did not continue atezo post-PD (median, 1.5 and 1.4 mo, respectively), and median post-PD atezo duration was 1.6 mo. Pts continuing atezo beyond PD had higher pre-PD ORR vs other groups (Table). 45 pts who continued atezo following initial PD (of 108 with post–first PD measurements) experienced decreases in target lesion SLD. OS data are in Table. In pts continuing atezo, pre- and post-PD exposure-adjusted tx-related AEs were similar (Table), with no related G5 AEs.

Conclusions: Pts who continued atezo beyond PD derived prolonged clinical benefit including tumor burden reduction and numerically longer OS vs pts who discontinued atezo post-PD in this single-arm study. Atezo was well tolerated throughout tx. An important future challenge in the post-PD setting will be to identify pts most likely to respond to atezo and appropriate sequencing of chemo agents thereafter.

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Table: 852PD Key baseline characteristics and outcomes in patients treated beyond ˚rst RECIST v1.1 PD

	ATEZO TREATMENT BEYOND PD (n = 137)	NO ATEZO BEYOND PD (n = 83)	NO ATEZO BEYOND PD (n = 83)	
			Other systemic tx (n = 19)	No systemic tx (n = 64)
Characteristic				
Median age	66 yr	67 yr	65 yr	68 yr
Male sex	80%	71%	63%	73%
Primary site: bladder	75%	75%	79%	73%
ECOG PS 0	43%	31%	42%	28%
Mets, visceral/liver	82%/27%	87%/41%	84%/42%	88%/41%
Response (with respect to study entry [baseline])				
Pre-PD RECIST v1.1 ORR	12%	1%	0%	2%
Post-PD RECIST v1.1 ORR	1%	0%	0%	0%
Overall survival				
Median follow-up duration (event/pt rate)	21.2 mo (70%)	20.0 mo (92%)	19.0 mo (90%)	20.0 mo (92%)
OS, median	12.8 mo	3.6 mo	8.8 mo	2.9 mo
18-mo OS	33.4%	3.9%	10.5%	1.7%
ppOS, median	8.6 mo	1.5 mo	6.8 mo	1.2 mo
12-mo ppOS	37.1%	2.7%	10.5%	0%
Treatment-related AEs, % (exposure-adjusted rate)				
All Gr: on/before PD (total of 18 pt-yr)	66% (512 per 100 pt-yr)	–	–	–
All Gr: after PD (total of 31 pt-yr)	53% (234 per 100 pt-yr)	–	–	–
Gr 3-4: on/before PD (total of 43 pt-yr)	9% (28 per 100 pt-yr)	–	–	–
Gr 3-4: after PD (total of 60 pt-yr)	9% (22 per 100 pt-yr)	–	–	–

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854PD Pazopanib (p) or sorafenib (s) + radium-223 (rad) in metastatic renal cell carcinoma (mrcc) with bone metastases (bm)

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Background: BM occur in 30% of patients (pts) with mRCC and are associated with symptomatic skeletal events (SSE) and worse outcomes with vascular-endothelial growth factor (VEGF)-targeted agents. Rad is a bone-seeking α-emitter that targets BM. We investigated the safety, efficacy and bone turnover markers (BTM) of Rad combined with P or S in pts with mRCC and BM.

Methods: 30 pts received therapy (15 treatment-naïve pts: P 800 mg/d +Rad; 15 treatment-refractory: S 400 mg BID +Rad). Rad was administered monthly for up to 6 infusions. The primary endpoint was BTM. Secondary endpoints included safety, SSE rate, time to SSE, objective response rate (ORR), narcotic use and survival.

Results: Of the 30 pts, 70% had clear cell histology, 17% were IMDC poor risk and 33% had liver metastases. Prior SSEs were reported in 100% and 65% of pts in the P and S cohorts, respectively. 1 pt had received denosumab. Median changes in BTM at cycle 2 and 4 compared to baseline are summarized in table and show declines in all BTMs. Best ORR by RECIST was partial response (PR) in 13% and stable disease (SD) 47%. Achieving > =50% decline in PINP at cycle 2 was associated with PR and SD (Fisher's exact p-value 0.01). Median treatment duration was 3.6 mo (IQR 1.5, 5.5). Progression-free survival was 8.2 mo [95%CI 5.6, NR] and 4.6 mo [95%CI 2.1, NR] in pts treated with P and S. Overall survival was 11.9 mo [95%CI 7.8, NR] and 8.7 mo [95%CI 6, NR], respectively. Overall rate of SSE on study was 47%; 67% in the P cohort (median time to SSE 6.3 mo [95%CI 3.6, NR]) and 27% in the S cohort (median time to SSE NR [95%CI 6.6 mo, NR]). There was no dose-limiting toxicity. The rate of treatment-related grade ≥3 toxicity was 39.3% including 3.6% grade 3 anemia.

Conclusions: Rad combined with P or S is safe and well tolerated. All BTMs significantly declined with Rad combined with P or S suggesting biologic activity in mRCC with BM. Randomized trials are needed to evaluate the role of Rad on SSE prevention in these pts.

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Table: 854PD

BTM	Baseline (IQR) N = 30	% change at cycle 2 median (IQR) N = 21	% change at cycle 4 median (IQR) N = 18
Bone-specific alkaline phosphatase (BALP)	11 (9, 16) ug/mL	−17 (-36, -7)	−23 (-32, -7)
Osteocalcin (OC)	16 (12, 19) ng/mL	−33 (-45, -21	−49 (-52, -31)
N-terminal propeptide of procollagen type I (PINP)	46 (30, 66) ug/mL	−57 (-63, -29)	−63 (-69, -44)
C-terminal cross-linked telopeptide of type I collagen (CTX)	432 (210, 595) pg/mL	−37 (-51, -1)	−34 (-49, -22)
N-terminal cross-linked telopeptide of type I collagen (NTX)	15 (11,21) nM BCE	−28 (-43, -7)	−28 (-43, -15)

855PD Adjuvant sunitinib (SU) in patients (pts) with high risk renal cell carcinoma (RCC): Safety and therapy management in S-TRAC trial

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Background: Pts with locoregional RCC at high risk (≥T3 and/or N+) of tumour recurrence post nephrectomy treated with adjuvant SU (50 mg daily; schedule 4/2) had significantly longer disease-free survival (DFS) vs. placebo (PBO; HR, 0.76; 95% CI, 0.59–0.98; P = 0.03). We report safety and therapy management data.

Methods: Reasons for SU treatment discontinuation (TDC), dose reduction (RED), dose interruption (INT), and pts TDC due to AEs by cycle, were summarized. Median time to SU TDC was calculated.

Results: Of the 615 pts enrolled, 306 were treated with SU at a median (range) daily dose of 45.9 (8.9–52.6) mg. 71% of pts remained on SU treatment for 9 months (mo) and 56% completed the full 1-year treatment. Most common reasons for TDC were AEs (28.1%) and relapse (7.2%) in SU arm, and relapse (19.4%) and AEs (5.9%) in PBO arm. Common AEs leading to TDC, RED and INT are summarized in the Table. TDC due to AEs in cycles 1, 3, 6, and 9, respectively: 7.8%, 3.3%, 2.6%, and 1.6% in SU arm, and 0.3%, 1.3%, 0.3%, and 0% in PBO arm. In the 86 pts who DC SU, median time to TDC was 4.5 mo. Median time to first RED and INT in SU-treated pts was 2.9 and 3.0 mo, respectively. Mean change from baseline in most PRO measures including Global Health Status for SU vs PBO was not clinically meaningful (difference, -4.76; 95% CI, -6.82, -2.71). More data, including time on RED/INT, time to onset of common AEs, and the impact of AEs on pts quality of life, will be presented.

Table: 855PD Most common AEs leading to TDC, dose RED and INT*

Treatment DC			Dose RED			Dose INT		
AE, %	SU	PBO	AE, %	SU	PBO	AE, %	SU	PBO
PPE	4.2	0	PPE	11.8	0.7	PPE	6.2	0
Hypertension	2.0	0	Fatigue	3.9	0.3	Hypertension	5.6	0
Asthenia	1.3	0	Diarrhoea	2.6	0	Neutropenia	5.2	0
Fatigue	1.0	0.3	Mucosal inflammation	2.6	0	Nausea	4.9	1.0
Pulmonary embolism	1.0	0.3	Neutropenia	2.6	0	Diarrhoea	4.6	1.3

*Many of the AEs leading to DC and INT were grade 1/2 TDC=treatment discontinuation; RED=reduction; INT=interruption; PPE=palmar-plantar erythrodysesthesia syndrome.

Conclusions: No new safety signals were identified with sunitinib use in the adjuvant RCC setting. Effective therapy management, including dose RED/INT if necessary, is important as it optimizes the possibility of receiving effective treatment.

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856P Avelumab treatment of metastatic urothelial carcinoma (mUC) in the phase 1b JAVELIN solid Tumor study: updated analysis with ≥6 months of follow-up in all patients

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Background: Avelumab, a human anti–PD-L1 monoclonal antibody, has shown promising efficacy and safety in patients (pts) with mUC. We report an updated analysis of avelumab treatment in 2 cohorts of pts from JAVELIN Solid Tumor (NCT01772004).

Methods: Pts with mUC whose disease had progressed after platinum-based therapy or were cisplatin ineligible received avelumab 10 mg/kg Q2W. Tumors were assessed every 6 weeks by independent review (RECIST v1.1). Endpoints included objective response rate (ORR), duration of response (DOR), progression-free survival (PFS), overall survival (OS), and safety (NCI CTCAE v4.0), and tumor PD-L1 expression. Kaplan-Meier (K-M) method was used to estimate DOR, PFS, and OS.

Results: As of Sep 2016, 249 pts had received avelumab and were followed for ≥6 mos (median 13.6 mos); 43 pts (17.3%) remained on treatment. 13 pts (5.2%) were cisplatin ineligible, including 7 (2.8%) platinum naïve. Confirmed ORR in all pts (n = 249) was 17.3% (95% CI 12.8–22.5; complete response in 4.4%) and the disease control rate was 44.6%. Response was ongoing in 34/43 pts (79.1%), median DOR was 20.1 mos (95% CI 9.7–20.1) and the K-M estimate of DOR of 6 mos was 92.7% (95% CI 79.1–97.6). In evaluable pts (n = 206), ORR in PD-L1+ and PD-L1– subgroups (≥5% tumor cell cut-off) was 25.6% and 13.7%, respectively. Median PFS was 1.6 mos (95% CI 1.4–2.7), median OS was 8.2 mos (95% CI 6.3–10.8), and the K-M OS rate at 12 mos was 41.9% (95% CI 34.8–48.7). 170/249 pts (68.3%) had a treatment-related adverse event (TRAE) of any grade, most commonly infusion-related reaction (23.3%) and fatigue (17.3%). 26 pts (10.4%) had a grade ≥3 TRAE, most commonly fatigue (1.6%), elevated lipase (1.6%), and pneumonitis (1.2%). 43 pts (17.3%) had an immune-related AE (grade ≥3 in 3.6%). 8 pts (3.2%) discontinued avelumab due to a TRAE. There was 1 treatment-related death (pneumonitis).

Conclusions: Avelumab showed durable clinical activity and had a manageable and tolerable safety profile in pts with mUC irrespective of PD-L1 expression. A phase 3 trial of avelumab as maintenance therapy after first-line platinum-based therapy for advanced UC is ongoing.

Clinical trial identification: NCT: NCT01772004 Protocol number: EMR 100070-001

Legal entity responsible for the study: Pfizer Inc., New York, NY, USA and Merck KGaA, Darmstadt, Germany

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857P Pembrolizumab (pembro) as first-line therapy in cisplatin-ineligible advanced urothelial cancer (UC): Outcomes from KEYNOTE-052 in senior patients (pts) with poor performance status

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Background: Advanced UC is most often seen in senior pts, in whom age-related complications such as renal dysfunction and poor performance status (PS) preclude ~50% from receiving standard first-line cisplatin treatment. In the phase 2 KEYNOTE-052 trial (NCT02335424), first-line pembro had clinically meaningful antitumor activity (ORR, 24%) and was well tolerated in cisplatin-ineligible pts with UC. Results from the subgroup of pts who were considered senior (≥65 y or ≥ 75 y) and had ECOG PS 2 are presented.

Methods: Pts were cisplatin ineligible and had advanced UC, measurable disease (per RECIST v1.1), ECOG PS 0-2, and no prior systemic chemotherapy. Pts received pembro 200 mg Q3W. Radiographic imaging was performed at wk 9, then Q6W for the first year, and Q12W thereafter. The primary end point was ORR (RECIST v1.1, independent radiology review).

Results: Of 370 pts, 302 (82%) were ≥65 y, 179 (48%) were ≥75 y, 120 (32%) were ≥65 y with ECOG PS 2, and 78 (21%) were ≥75 y with ECOG PS 2. Median follow-up was 5 mo. ORR (95% CI) was similar to that reported in the overall study population regardless of age cutoff (Table). Poor PS did not impact ORR in senior pts (Table). 6-mo PFS rates were consistent across senior groups (Table). 64% (≥65 y), 66% (≥75 y), 58% (≥65 and ECOG PS 2), and 64% (≥75 y and ECOG PS 2) of pts experienced treatment-related AEs. 16% of pts ≥65 and ≥75 y and 17% of pts ≥65 and ≥75 y with ECOG PS 2 experienced grade ≥3 treatment-related AEs.

Conclusions: Results from subgroup analyses of senior pts with poor PS in KEYNOTE-052 confirm that first-line pembro elicits clinically meaningful responses consistent with the overall study population. Pembro is well tolerated in cisplatin-ineligible pts with UC, including those who are senior with poor PS.

Clinical trial identification: NCT02335424; January 7, 2015

Legal entity responsible for the study: Merck & Co., Inc.

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858P Sacituzumab govitecan (IMMU-132) for patients with pretreated metastatic urothelial uancer (UC): interim results

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Background: Pts with metastatic UC have limited therapy options. Immune checkpoint inhibitors (CPI) are now given to patients with advanced UC, but only about 25% respond. We are studying the safety and efficacy of sacituzumab govitecan (IMMU-132), an anti-Trop-2/SN-38 antibody-drug conjugate, in pts with UC refractory to other therapies.

Methods: In this phase I/II study (NCT01631552), pts with metastatic UC who progressed after ≥1 prior systemic therapy were treated with IMMU-132 at 10 mg/kg on days 1 and 8 of 21-day cycles, until progression or unacceptable toxicity. All intention-to-treat (ITT) pts, including those who relapsed/progressed after CPI therapy, are evaluated for safety, ORR by RECIST 1.1 (confirmed PR/CR), PFS, and OS. Response-evaluable (RE) pts received ≥ 2 doses and ≥ 1 post-baseline CT (RECIST 1.1) assessment.

Results: 41 pts (39M/2F; median age 68 y, range 50-91) were enrolled (RE = 36); ECOG 0/1: 31%/69%; median of 3 (range 1-6) prior therapies, including 34/41 platinum and 15/41 CPI regimens. Metastatic sites: lymph node 68%, lungs 54%, liver 32%, bone 27%; overall visceral disease, 31/41 (76%). Pts received a median of 12 (range 1-58) doses. ORR in the ITT population was 34% [14/41 (1 CR, 13 PR); ORR was 39% in the RE group, including 5/13 (39%) with liver mets]; 14 SD (39%); 8 PD (20%), and 5 inevaluable. In responders, 13/14 had prior platinum, 8/14 (57%) ≥3 prior therapies, and 4 prior CPI [4/13 in the RE group (31%), where IMMU-132 was ≥4th line of therapy in 11/13 pts]. Median time to response: 1.9 mos. Median duration of response: 12.9 mos (95%CI, 5.1-12.9), with 8/14 continuing therapy. Clinical benefit rate (CR+PR+SD≥6 mos) is 44%; 56% for SD ≥ 4 mos. In the 41 ITT pts, median PFS and OS are 7.2 (95% CI, 5.0-10.7) and 15.5 mos (95% CI, 8.9-17.2), respectively. Grade ≥3 adverse events ≥5% were 28% neutropenia, 9% febrile neutropenia, 9% fatigue, 9% anemia, 6% diarrhea.

Conclusions: With an ITT ORR of 34%, PFS of 7.2 mos, OS of 15.5 mos, and duration of response of 12.9 mos in 41 unselected pts with advanced pretreated UC (median of 3 prior therapies), these interim results show IMMU-132 is a promising agent in pts relapsed/refractory to chemotherapy and immune checkpoint inhibitors.

Table: 857P Efficacy Outcomes

	≥65 y n = 302	≥75 y n = 179	≥65 y and ECOG PS 2 n = 120	≥75 y and ECOG PS 2 n = 78
ORR, % (95% CI)	23 (19-28)	23 (17-30)	24 (17-33)	27 (18-38)
CR	4 (2-7)	2 (1-6)	2 (0.2-6)	3 (0.3-9)
PR	19 (15-24)	21 (15-27)	22 (15-31)	24 (15-35)
6-mo PFS, %	30%	27%	28%	27%

Clinical trial identification: NCT01631552

Legal entity responsible for the study: Immunomedics, Inc.

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Disclosure: S.T. Tagawa: Received honoraria for consulting from Immunomedics; Weill Cornell has received research funding from Immunomedics. B. Faltas: Weill Cornell received research funding from Immunomedics, Inc. P. Maliakal, B. Mudenda, R. Sharkey, W. Wegener, D. Goldenberg: Employed by Immunomedics, Inc. All other authors have declared no conflicts of interest.

859P Anti-tumor activity of the pan-FGFR inhibitor rogaratinib in patients with advanced urothelial carcinomas selected based on tumor FGFR mRNA expression levels

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Background: Fibroblast growth factor receptor (FGFR) signaling is deregulated in urothelial carcinomas (UC). Rogaratinib is an oral inhibitor of FGFRs 1-4 with demonstrated antitumor activity in bladder cancer xenograft models. We report the results from a rogaratinib phase I trial expansion cohort in UC patients selected based on FGFR1-3 mRNA tumor overexpression and/or presence of activating mutations in the FGFR3 gene.

Methods: Patients with locally advanced or metastatic UC who have progressed or ineligible for standard therapy were screened for high FGFR1-3 mRNA expression levels by RNA *in situ* hybridization (RNAscope®) and Nanostring® assays utilizing fresh or archival FFPE tumor specimens. FGFR3-activating mutations were evaluated by a PCR based assay (Qiagen). Patients were treated with rogaratinib 800mg BID on a continuous regimen. Tumor response was assessed by RECIST, v1.1. Adverse events were classified using CTCAE v4.03 criteria.

Results: Biopsies from a total of 109 patients with advanced UC were screened, with 42.3% found to be FGFR positive; of which 87% due to FGFR3 mRNA overexpression, 4% FGFR1, and 9% mixed FGFR isoform mRNA expression. Co-ocurrence of FGFR3-activating mutations and high FGFR3 mRNA expression was seen in 8% of patients. Among 20 patients with UC treated with rogaratinib, 16 (75%) had tumor shrinkage in target lesions with 9 (45%) showing tumor shrinkage of more than 20%, and 6 (30%) having a partial response (PR). Disease control rate (CR+PR+SD>12w) was 75%. Three patients with a PR had elevated tumor FGFR3 mRNA levels without corresponding genomic alterations. The most frequent AEs were hyperphosphatemia and diarrhea.

Conclusions: Selection of UC patients for treatment with rogaratinib based on FGFR1-3 mRNA expression levels in archival tissue was feasible and identified patients benefitting from treatment without having aberrations of FGFR-encoding genes. Rogaratinib has a favorable safety profile and showed anti-tumor activity in biomarker-selected UC patients which warrants further clinical development.

Clinical trial identification: NCT01976741

Legal entity responsible for the study: Bayer AG

Funding: Bayer AG

Disclosure: M. Schuler: Consultant: AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Lilly, Novartis, Roche; Honoraria: Alexion, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Lilly, Novartis Research: Boehringer Ingelheim, Bristol Myers-Squibb, Novar. S. Bender, M. Ocker, H. Nogai, A. Wagner, P. Ellinghaus: Employment: Bayer AG. S. Ince: Employment: Bayer HealthCare Pharmaceuticals. All other authors have declared no conflicts of interest.

860P Phase II California cancer consortium trial of gemcitabine-eribulin combination (ge) in cisplatin ineligible patients (pts) with metastatic urothelial carcinoma (mUC): Efficacy report (NCI-9653; 1UM1CA186717, NO1-CM-2011-00038)

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Background: Cisplatin-based regimens are the mainstay of treatment (tx) for mUC. Unfortunately, pts with mUC are often elderly and have comorbid conditions that preclude cisplatin-based tx. This CTEP-sponsored trial seeks to assess the efficacy and tolerability of GE in this population.

Methods: A Simon 2 stage design was employed (7 + 14). To proceed to full accrual first stage required 2 or more confirmed responders- complete (CR) or partial (PR) response. To be a positive trial, 7 responders were required. Tx consisted of Gemcitabine 1gm/m2 and Eribulin 1.4mg/m2, both on Day (D) 1 and D8 of a 21-D cycle and continued until progression (PD) or unacceptable toxicities. Cisplatin ineligibility was defined as creatinine clearance (CrCl) <60 (but ≥30) ml/min, grade 2 neuropathy, or grade 2 hearing loss.

Results: Between 6/2015 and the report cutoff date of 5/2017, 24 eligible pts with a median age of 73 (range: 62-88) were enrolled. Demographics: 20 males, 4 females. ECOG performance status of 0/1/2 was seen in 11/11/2 pts. Sites of disease included: nodes 16, lungs 8, liver 7, bladder 5, bones 2. Median number of cycles was 3.5 (range 1-16). 2+ confirmed PRs in the first 7 pts allowed the trial to proceed to full accrual. Of 19 evaluable pts, 2 had a CR, 10 had a PR, 5 had SD and 1 had PD. The objective response rate (ORR) was 63%. Overall survival (OS) 14.9 months (5.6, 21.9+) and progression free survival (PFS) was 6.9 months (5.3, 16.1+). Duration of response (DOR) was 4.6 months (range: 0.5, 15.0). Among the first 21 pts 7 had a PR and 2 had a CR and 5 were inevaluable for response, with an ORR of 43%. All 24 pts were evaluable for toxicities; the most common any grade toxicities included fatigue 83%, neutropenia 75%, anemia 63%, alopecia 50%, elevated AST 46%, constipation and nausea 42% each and thrombocytopenia 36%.

Conclusions: GE exceeded the threshold for efficacy in this trial. The endpoints of ORR, OS and PFS compare favorably to the commonly used regimens in this setting such as gemcitabine-carboplatin with a confirmed ORR of 36.1% and OS of 9.3 months. These data support further development of this combination in pre-and post immunotherapy settings.

Clinical trial identification: NCI-9653

Legal entity responsible for the study: NCI

Funding: None

Disclosure: All authors have declared no conflicts of interest

861P Expression of long non-coding RNA MFI2-AS1 is a strong predictor of recurrence in sporadic localized clear-cell renal cell carcinoma

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Background: Improved patient stratification is a challenge in adjuvant clear-cell renal cell carcinoma (ccRCC) trials. Long non-coding RNAs (lncRNAs) are genome-wide regulators with potent prognostic value. We aimed to predict risk of ccRCC recurrence based on lncRNA expression from two independent cohorts.

Methods: Identification of prognostic lncRNAs was performed in a training set of 351 samples of localized ccRCC from the Cancer Genome Atlas, using Cox regression based on disease-free (DFS) and overall survival. Functional annotation of differentially expressed genes according to lncRNA expression was performed. The validation cohort included 167 localized ccRCC patients. Gene expression was studied by qRT-PCR. Kaplan-Meier estimators and Cox regression models were used for survival and multivariate analyses. Primary endpoint was DFS.

Results: MFI2-AS1 was best candidate lncRNA in the developmental study. Its expression was associated with immune response genes expression. In the validation cohort, MFI2-AS1 expression was associated with shorter DFS (Hazard Ratio (HR) for relapse 3·5, $p = 0·0001$), independently from Leibovich recurrence classification and grade. Combined with Leibovich classification, MFI2-AS1 status improved prediction of recurrence, with a C-index of 0·70 compared to 0·67 for MFI2-AS1 alone and 0·66 for Leibovich classification alone. In patients with aggressive tumors (Leibovich ≥ 5), MFI2-AS1 expression was associated with a dramatically increased risk or relapse (HR 12·16, $p < 0·0001$) compared to patients with undetectable MFI2-AS1 who had ultimately favorable outcomes. MFI2-AS1 expression was also correlated with high tumor burden.

Conclusions: MFI2-AS1 is a potent predictor of recurrence in localized ccRCC. Combined with historical classifications, it provides a highly accurate patient stratification that may be useful in adjuvant settings.

Legal entity responsible for the study: Gabriel G Malouf, MD, PhD. Fondation Avec & Hôpital Salpêtrière, Department of Medical Oncology, Paris, France

Funding: Fondation Avec

Disclosure: N. Tannir: Honoraria and consulting: Bristol-Myers Squib, Exelixis, Nektar, Novartis, Pfizer, Argos, Calithera. Research funding: Bristol-Myers Squib, Exelixis, Epizyme, Novartis, Miranti. All other authors have declared no conflicts of interest.

862P Treatment and outcome after Immune checkpoint inhibitors (ICI) in metastatic Urothelial Carcinoma (mUC): A European perspective

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Background: PD-1/PD-L1 inhibitors are changing the current landscape of mUC. Outcomes after discontinuation of ICI are unclear in this population.

Methods: Data from 8 European institutions was retrospectively collected. Target population was patients progressing on ICI. Univariate and multivariate analysis for overall survival (OS, calculated from the last date of ICI until death from any cause) as well as potential predictive factors of response to post-progression therapy (ppT) were performed. Tests were two-sided.

Results: From March 2013 to April 2017, 291 patients were identified. 227 (78%) experienced progression (PD) on ICI. Median post-progression OS of ICI was 5 months (95% CI 3.7-6.3), being 8.6 (95%CI 7.5-9.7) if receiving ppT vs 1.8 (95%CI 1.5-2.1) if best supportive care alone ($p < 0.001$, HR 0.23, 95%CI 0.16-0.32). OS increased according to number of lines received after PD ($p < 0.001$, HR 0.29, 95%CI 0.21-0.39). In the multivariate analysis, shorter duration of ICI, visceral metastases and female sex correlated with worse OS. Prior response to ICI was associated with improved OS in the univariate analysis only. Use of cisplatin-based chemotherapy, location of primary tumor, histology and age did not modify OS. Of patients progressing on ICI, 95 (42%) received subsequent treatment: 84% had 1 systemic line, 14% 2, and 2% 3 lines. RR to 1st ppT was 49% vs 21% for 2nd line or beyond. Median OS was 7.8 months when 1 line of therapy was received after ICI (95%CI 6.6-8.9) vs 18 (95%CI 8.5-27.4) when 2 or more (HR 0.29, p 0.02). Prior exposure to CT (OR 0.19, $p = 0.003$) and shorter duration of ICI (OR 0.24, $p = 0.012$) were correlated with worse RR in the multivariate study. Prior exposure to chemotherapy (CT) did not impact in the OS of these patients. RR to 1st line CT was 56% when used before exposure to ICI vs 66% when used after (p 0.3). Details on patient characteristics, univariate and multivariate analysis will be presented.

Conclusions: Many patients do not receive subsequent chemotherapy, including CT-naive patients. Patients who receive post-ICI therapy have good outcomes. ICI does not appear to confer resistance to CT. Retrospective analysis is prone to bias.

Legal entity responsible for the study: Alfonso Gómez de Liaño Lista

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863P Phase 2 study of pembrolizumab alone or combined with acalabrutinib in platinum-refractory metastatic urothelial carcinoma (mUC)

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Background: PD-1/PD-L1 inhibitors have shown clinical benefit in mUC; however, the ORR is 15-25%, highlighting the need for more effective therapies. Gunderson, et al

Table: 863P

	Pembrolizumab n = 35	Pembrolizumab + acalabrutinib n = 40
Safety, n (%) (excluding events after cross over)		
Any grade 3-4 AE	17 (49)	29 (73)
Any treatment-related grade 3-4 AE	6 (17)	21 (53)
Any grade 3-4 SAE	12 (34)	20 (50)
Any treatment-related 3-4 SAE	0 (0)	6 (15)
AE leading to study drug discontinuation	7 (20)	15 (38)
Grade 5 AE	0 (0)	3 (8)
Treatment-emergent AEs, n (%) (any grade, ≥30% of all pts)		
Fatigue	16 (46)	33 (83)
Decreased appetite	13 (37)	17 (43)
Diarrhea	7 (20)	15 (38)
Anemia	7 (20)	14 (35)
Vomiting	10 (29)	12 (30)
Ef˚cacy		
ORR, % (95% CI) [n/N]		
Overall population	26 (13, 43) [9/35]	20 (9, 36) [8/40]
PD-L1+ population	23 (8, 45) [5/22]	22 (9, 42) [6/27]
Median PFS, mo (95% CI)	1.6 (1.4, 4.2)	2.2 (1.4, 3.5)
Median OS, mo (95% CI)	11.4 (5.7, NE)	6.3 (3.6, 12.3)
12 mo OS, % (95% CI)	44.1 (27.2, 59.8)	38.5 (23.5, 53.3)

AE, adverse event; CI, confidence interval; mo, month; NE, not estimable; ORR, overall response rate; PFS, progression-free survival; SAE, serious adverse event; OS, overall survival.

2015 showed activation of Bruton tyrosine kinase (BTK) in myeloid cells of the pancreatic tumor microenvironment. As myeloid suppression impairs T-cell anti-tumor function, BTK inhibition may augment checkpoint inhibitor T-cell activation. This study assessed safety and efficacy of the PD-1 inhibitor pembrolizumab (P) alone or with the BTK inhibitor acalabrutinib (PA) in mUC.

Methods: Patients (pts) with mUC who progressed with ≥1 line of platinum chemotherapy were randomized 1:1 to P (200 mg Q3W IV) or PA (200 mg Q3W+100 mg BID PO). Pts who progressed (irRECIST) with monotherapy were permitted to cross over to combination therapy. Primary objectives were safety and ORR (local review, RECIST 1.1). Secondary endpoints included PFS and OS. Tumor PD-L1 expression was evaluated by Q^2Solutions.

Results: Between Jun 2015 and Jan 2016, 75 pts were treated with P (n = 35) or PA (n = 40); cross over, n = 10. Median age, 66 y; men, 76%; ECOG PS 0-1, 97%; median prior therapies, 2 (range, 1-4). In P/PA median (mos) time on study treatment, 2.96/1.94; median follow-up, 11.2/6.1. Grade 3-4 treatment-emergent AEs (%) in ≥ 15% of P or PA was anemia (20) in P and fatigue (23), increased alanine aminotransferase (23), urinary tract infection (18), and anemia (15) in PA. There were 3 fatal AEs in PA: hemoptysis and sepsis (unrelated); pneumonia (P-related). ORR was 26% (CR, 9%) with P and 20% (CR, 10%) with PA. Median PFS was similar between treatment arms; median OS was 11.4 and 6.3 mos in P vs PA (Table). Most pts (49/60) had PD-L1+ tumors; expression was not associated with improved ORR (Table).

Conclusions: Most pts tolerated the study treatment, although more PA-treated pts had grade 3-4 AEs. Acalabrutinib plus pembrolizumab did not improve ORR over pembrolizumab alone in pts with mUC, regardless of PD-L1 status.

Clinical trial identification: NCT02351739

Legal entity responsible for the study: Acerta Pharma

Funding: Acerta Pharma

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864P Long non-coding RNAs are differentially expressed between bladder cancer subtypes

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Background: The recent identification of molecular bladder cancer subtypes by whole transcriptome studies showed similarities to molecular breast cancer phenotypes. We here validate these subtypes with a sensitive 36 gene nCounter screening and analyse relevant lncRNA for their differential expression.

Methods: RNA has been extracted from chemotherapy-naïve muscle-invasive bladder cancer (MIBC) after radical cystectomy (follow-up: 12 years, n = 48). A multiple marker gene panel has been quantified with the nCounter technology. *In silico* validation of the classifier geneset on 170 MIBCs has been performed. All squamous carcinoma were excluded. LncRNAs were analyzed in a clustering-independent assessment. Multivariate analyses were performed by a Cox proportional hazards model.

Results: 36 consensus genes were generated by Venn diagrams based on the Mannheim, Lund, Chungbuk and MDA cohorts. This minimal set of genes generated 3 stable clusters: basal, luminal and infiltrated. The subtype specific assessment of 14 lncRNAs relevant in bladder cancer showed a highly subtype specific expression for 9 lncRNAs. The infiltrated subtype, characterized by an activated p53 downstream signature, showed an overexpression of SRA1 and MEG3 ($p \leq 0.003$) - the latter is known for promoting the expression of TP53. The lncRNAs H19, GAS5, TUG1 and CBR3-AS1 showed a significant upregulation in the luminal subtype ($p < 0.05$) whereas SNHG16 showed an exclusive suppression. MALAT1 was suppressed in the basal subtype. A distinct cutoff of the lncRNA H19 allowed a risk stratification into high- and low-risk patients. The luminal subtype and H19 were the only independent risk factors in multivariate analysis adjusted for TNM and were predictive for a 3- to 4-fold higher risk of death ($p < 0.03$).

Conclusions: In this study, MIBC subtypes have been validated by a sensitive quantification method. Molecular subtypes and H19 prove to be independent risk factors superior to TNM. This study demonstrates for the first time a differential expression of lncRNA between MIBC subtypes. The potential impact of lncRNA on phenotype determination has to be investigated in vivo.

Legal entity responsible for the study: BRIDGE Consortium

Funding: None

Disclosure: R. Sébastien: Novartis Research Fund. All other authors have declared no conflicts of interest.

865P Adjuvant chemotherapy after radical nephroureterectomy does not improve survival in patients with upper tract urothelial carcinoma: A joint study of the EAU-Young Academic Urologists and the Upper Tract Urothelial Carcinoma Collaboration

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Background: In patients (pts) with upper tract urothelial carcinoma (UTUC) the benefit of adjuvant chemotherapy (ACT) after radical nephroureterectomy (RNU) is debated. We aimed to analyze the benefit of ACT vs observation (Obs) in an international study.

Methods: Data from 15 centers was collected, totalling 1,544 pts, treated between 2000 and 2015. Criteria for pt selection were: UTUC diagnosis, pT2-4N0/x and/or pN+ stage undergoing RNU. The standardized differences (SD) approach was used to compare subgroup characteristics. Overall survival (OS) was the primary endpoint. The adopted propensity scores (PS) techniques included 1:1 PS matching and inverse probability of treatment weighting (IPTW). Additionally, the IPTW analysis was performed with the inclusion of the covariates, i.e. with doubly robust estimation (DREP). 6-month landmark analysis (LA) was also performed.

Results: A total of 312 pts received ACT and 1,232 observations. Despite differences between the two groups, SD was generally <10% after matching. In the DREP-adjusted comparison, ACT was significantly associated with shorter OS (HR: 1.25, 95%CI: 1.02-1.54, p = 0.032), while no difference was observed in the matched analysis (HR: 1.14, 95%CI: 0.91-1.43, p = 0.268, table). These findings were confirmed in subgroup analyses (pT2N0/x; pT3-4N0/x; pTanyN+), and after LA. Relapse-free survival outcomes were overlapping to OS in the matched analyses (ACT, HR: 1.59 (95%CI: 1.25-2.02, $p < 0.001$). The limitations of the retrospective studies should be acknowledged.

Conclusions: ACT does not improve OS compared to Obs in pT2-4 and/or pN+ UTUC. These findings contribute to the uncertainties regarding ACT in UTUC and further support the need for dedicated prospective trials in UTUC, new more potent therapies, and enhanced pt selection criteria.

Legal entity responsible for the study: Andrea Necchi

Funding: None

Disclosure: All authors have declared no conflicts of interest.

Table: 865P Results of the Cox analyses for the OS endpoint

Unadjusted comparison (N = 1,544): Covariate	HR	Lower 0.95	Upper 0.95	p-value
Group: ACT vs. No ACT	1.44	1.21	1.72	<0.001
Matched analysis (N = 570):				
Group: ACT vs. No ACT	1.14	0.90	1.43	0.268
Propensity score-adjusted comparison (ATE approach, N = 1,544):				
Group: ACT vs. No ACT	1.31	1.08	1.58	0.005
Doubly-robust procedure (ATE approach, N = 1,544):				
Group: ACT vs. No ACT	1.26	1.02	1.54	0.032
Age: 75 vs. 61	1.33	1.18	1.49	<0.001
ECOG-PS: 1 vs. 0 2 vs. 0	1.37 1.61	1.18 1.20	1.58 2.16	<0.001
Pathologic stage: pT3-4N0 vs. pT2N0 pTanyN+ vs. pT2N0 pT2Nx vs. pT2N0 pT3-4Nx vs. pT2N0	1.30 2.97 0.92 1.72	0.99 2.26 0.69 1.36	1.71 3.90 1.20 2.19	<0.001

Abbreviations: ACT: adjuvant chemotherapy; ATE: average treatment effect; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; HR: hazard ratio; OS: overall survival.

866P Impact of cisplatin-based therapy on long-term survival in advanced urinary tract cancer (aUTC). A retrospective international study of invasive/advanced cancer of the urothelium (RISC)

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Background: Cisplatin-based chemotherapy is the treatment of choice in aUTC. Nevertheless, about 50% of patients are unfit for this treatment. Long-term survival of patients with aUTC has not been adequately studied outside the context of clinical trials. In addition, the impact of cisplatin utilization on long-term survival has not been adequately addressed. We used a multinational database to study long-term survival and the impact of treatment type in unselected aUTC patients as well as to provide benchmarks for future trials.

Methods: Selection criteria: Diagnosis of aUTC, non small-cell histologies, administration of 1st-line chemotherapy, survival data available. Major end point: Overall survival (OS). Fitness-for-cisplatin (FFC) was defined according to Galsky et al (2011). Landmark and conditional survival analysis was used to study the change of prognosis with time from initiation of 1st-line chemotherapy.

Results: 1361 patients (median fup: 31 months) were analysed. Survival analyses are shown in the table.

Cisplatin therapy and FFC were associated with improved long-term survival. FFC patients have a 28% probability of 5-year survival, which is increased to 74% for the 34% of patients who survive 3-years after initiation of cisplatin-based chemotherapy.

Conclusions: Published criteria for FFC accurately predict for long-term survival of aUTC patients, following cisplatin-based chemotherapy, while patients not treated with cisplatin have inferior outcome. Probability of long-term survival was increased with time after initiation of 1st-line (cisplatin or no-cisplatin) therapy.

Legal entity responsible for the study: RISC investigators

Funding: None

Disclosure: Y-N. Wong: The author was at Fox Chase Cancer Center at the time the study was conducted but is now a Janssen Scientific Affairs employee. All other authors have declared no conflicts of interest.

Table: 866P

	Probability of surviving (y) (%)		
	3	4	5
Received Cisplatin (n = 689) Did not receive cisplatin (n = 672)	28 13	23 10	19 6
FFC (n = 421) Unfit (n = 550)	28 13	22 10	18 8
Received Cisplatin/Fit (n = 295) Did not receive cisplatin/unfit (n = 368)	34 11	28 10	28 6
	Probability of surviving 2 more years having lived (y) (observed/predicted) (%)		
	1	2	3
Received Cisplatin Did not receive cisplatin	44/43 30/32	54/62 48/47	62/67 43/57
FFC Unfit	45/43 31/32	64/60 56/53	64/69 61/66
Received Cisplatin/Fit Did not receive cisplatin/unfit	49/49 29/32	67/65 57/55	82/74 58/68

867P Correlation of circulating tumor DNA (ctDNA) assessment with tissue-based comprehensive genomic profiling (CGP) in metastatic urothelial cancer (mUC)

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Background: Tissue-based CGP reveals a multitude of actionable targets in patients (pts) with mUC (Ross et al Cancer 2015). Assessment of ctDNA from blood offers the benefit of avoiding risks of biopsy/surgery and allows for serial assessment.

Methods: In pts with mUC, 50-100 ng of ctDNA was extracted from plasma during routine clinical care. Using adapted sequencing libraries, hybrid capture and sample multiplexed sequencing was performed with an Illumina HiSeq 2500 platform to a median coverage depth of 6353X. This CLIA-certified test of 62 genes detected genomic alterations (GAs) at low allele frequencies (0.1% for substitutions, 1% for indels/rearrangements and 20% for copy number amplification). In several pts CGP data was available from separate tissue-based CLIA-certified tests for which methods have been previously reported (Frampton *et al* Nat Biotechnol 2013). In addition to examining intra-patient differences, we compared the cumulative frequency of GAs in ctDNA to a large pool of tissue-based CGP in pts with mUC (n = 2024).

Results: 27 pts (18:9 M:F) with mUC had ctDNA assessment; median age 68 (range, 52-86). There was evidence for ctDNA in the blood for 25/27 pts (93%), and at least 1 GA was observed in 20/27 (74%) cases. The most frequently altered genes were TP53 (63%), TERT-promoter (33%), PIK3CA (15%), FGFR3 (11%), NF1 (11%) and ERBB2 (7%). With the caveat of a limited sample size, the cumulative frequency of selected clinically relevant GAs was distinct in ctDNA and tissue. The frequency of FGFR3 alteration was lower in ctDNA as compared to tissue (11% vs 23%), as was the frequency of ERBB2 alteration (14% vs 7%). A pt with FGFR3 GA in baseline tumor tissue showed disappearance of FGFR3 GA and evolution of a TP53 alteration in ctDNA following treatment with an FGFR3 inhibitor. In a pt with ERBB2 and TP53 GAs in baseline tumor tissue, ctDNA collected at the time of resistance to cisplatin-based therapy showed persistence of ERBB2 and TP53 GAs and a new NF1 GA.

Conclusions: Using hybrid capture-based genomic profiling of ctDNA, ctDNA was detected in the vast majority of pts with mUC. Utility was demonstrated through detection of potential resistance mutations in pts receiving chemotherapy and targeted agents.

Legal entity responsible for the study: Siraj Ali

Funding: None

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868P Comparison of circulating tumor DNA (ctDNA) profile in metastatic urothelial carcinoma (mUC) derived from the upper tract (UT) and lower tract (LT)

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Background: We have previously reported ctDNA profile in 246 patients (pts) with mUC derived from the LT (mLTUC) (Grivas et al ASCO GU 2017). mUC derived from the UT (mUTUC) is a clinically distinct entity with a more aggressive disease course. The ctDNA profile of mUTUC has not been previously characterized.

Methods: Data was obtained from pts with mUTUC who received ctDNA profiling as a part of routine clinical care using a CLIA-certified, CAP-accredited platform evaluating up to 70 genes. Genomic alterations (GAs) were pooled for the entire cohort. Comparison to the previously reported mLTUC was performed using the chi-square test.

Results: Between Oct 2014 and Apr 2017, ctDNA results from 75 pts (M:F 30:45) with mUTUC were assessed. Median age of the cohort was 69 (range, 40-90). A median of 6.2 months had elapsed from the time of diagnosis with mUC and ctDNA assessment. Genomic alterations (GAs) were detected in 71 pts (95%), with an average/median of 4.5/3 GAs per pt (range, 0-35). Treatment related data was available in 30 pts (40%). The frequency of GAs in mUTUC vs mLTUC was as follows: TP53 (51% vs 52%), PIK3CA (20% vs 18%), ARID1A (16% vs 17%), EGFR (8% vs 13%), ERBB2 (8% vs 7%), FGFR3 (7% vs 11%), BRCA2 (6% vs 7%) and NF1 (6% vs 8%) (P=NS for all comparisons). Alteration types were diverse; for instance, FGFR3 alterations included fusion (FGFR3-TACC3 [n = 5]) and mutation (S249C [n = 3] and Y373C [n = 2]). Correlation of ctDNA profile with treatment and clinical outcome will be presented at the meeting.

Conclusions: Despite representing a clinically distinct entity, mUTUC demonstrated a ctDNA profile similar to that of mLTUC. These data may inform the design of clinical trials of targeted therapy (e.g., FGFR3 and ERBB2 inhibitors) in mUC, suggesting that inclusion of both mUTUC and mLTUC may be warranted.

Legal entity responsible for the study: Neeraj Agarwal

Funding: None

Disclosure: L.A. Kiedrowski: LAK is an employee of Guardant Health. R.J. Nagy: RJN is an employee of Guardant Health. K. Banks: KB is an employee of Guardant Health. R. Lanman: RL is an employee of Guardant Health. All other authors have declared no conflicts of interest.

869P Modeling of Tumor Kinetics and Overall Survival to Identify Predictive Factors for Efficacy of Durvalumab in Patients with Urothelial Carcinoma (UC)

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Background: Durvalumab is a human mAb that binds to PD-L1 and blocks its interaction with PD-1 and CD80. The objectives of this analysis were to describe the longitudinal tumor size profiles, identify factors predicting tumor growth and regression, and associate tumor kinetics with overall survival (OS).

Methods: Longitudinal tumor size and OS data obtained from UC patients (Study 1108; NCT# CD-ON-MEDI4736-1108) who received durvalumab were analyzed using a nonlinear mixed effect model that describe tumor growth, tumor killing, and delay in immune response leading to tumor killing. An OS model was developed by linking model-predicted tumor size over time to survival hazard in a constant hazard model. Potential predictive factors of tumor growth and regression, as well as survival were evaluated in a multivariate covariate analysis in the tumor kinetic and OS model, respectively.

Results: Tumor kinetic and OS models adequately described the longitudinal tumor size and survival data from UC patients. The most influential factor associated with more rapid tumor growth was high baseline neutrophil-to-lymphocyte ratio (NLR), while lymph node disease was associated with decreased growth rate. Tumor (TC) or immune cell PD-L1 expression (IC), baseline tumor size and liver metastasis were identified as predictive factors for tumor killing. Simulations showed increased response rates with higher TC and/or IC (by 6/9%, and 18/24%, with 25% and 50% cutoff for TC/IC, respectively). After accounting for tumor response, the risk of death decreased with higher TC/IC and lower baseline hemoglobin and albumin levels, while liver metastasis, lymph node disease, and prior carboplatin treatment were associated with higher risk.

Conclusions: Tumor kinetic modeling identified factors that predict tumor growth and shrinkage following durvalumab therapy in UC patients, and permits investigation of predictive biomarker strategies considering confounding factors. Joint modeling that associates predicted tumor kinetics with OS allows model-based extrapolation of missing data and evaluation of other factors influencing OS after accounting for change in tumor size over time.

Clinical trial identification: NCT01693562 (September 14, 2012)

Legal entity responsible for the study: MedImmune

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870P Expression of Galectin-1 Determines Tumor Recurrence and Cancer-specific Survival in Patients with pT3 Upper Urinary Tract Urothelial Carcinoma

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Background: Upper urinary tract urothelial carcinoma (UTUC) is an aggressive and lethal disease. For patients with locally advanced UTUC, recurrence of tumor is frequent, and lacks of predictive biologic markers limited the choice of postoperative treatment. Galectin-1 (GAL1) is a β-galactoside-binding protein, participating in many parts of tumorigenesis, including cell proliferation, invasiveness, metastasis, and angiogenesis. However, the role of GAL1 in UTUC has not been fully investigated. The aim of this study was to examine the prognostic impact of GAL1 in patients with UTUC.

Methods: The study enrolled 86 UTUC patients who underwent radical nephroureterectomy and bladder cuff excision with final pathologically diagnosed as pT3N0 stage between January 2005 and December 2012. Perioperative characteristics and pathologic features were recorded. Immunohistochemical staining of tumor specimens using anti-GAL1 antibody were performed. UTUC cell line (BFTC-909) was used for *in vitro* study of tumor invasiveness and migration. Kaplan-Meier analyses and Cox proportional regression models were used for univariate and multivariate survival analyses.

Results: Using 10% expression of GAL1 protein as a cuff-off point, the study population could be classified as GAL1-high (GAL1 $>$ 10%, n = 35) or GAL1-low (GAL1 $\leq$ 10%; n = 51) group. Basic clinicopathologic characteristics were comparable between two groups. In univariate analysis, high GAL1 expression was significantly associated with a worse recurrence-free survival (RFS; $p = 0.028$) and cancer-specific survival (CSS; $p = 0.025$). Multivariate analysis showed GAL1-high is an independent factor for RFS (HR 2.43; 95% CI 1.17-5.05, p = 0.018) and CSS (HR 4.04; 95% CI 1.25-13.03, p = 0.019). In vitro study, we found that knockdown of GAL1 reduced UTUC cancer cell migration and invasion significantly.

Conclusions: Galectin-1 expression is a reliable prognostic factor for locally advanced UTUC. GAL1 inhibition may serve as a potential therapeutic target for patients with UTUC.

Legal entity responsible for the study: Yu-Li Su

Funding: None

Disclosure: All authors have declared no conflicts of interest.

871P Identification of genomic features underlying response of muscle-invasive bladder cancer (MIBC) to neoadjuvant sorafenib, gemcitabine, and cisplatin (SGC) in an open-label, single-arm, phase 2 study

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Background: Genomic analyses demonstrated that MIBC can be grouped into molecular subtypes that portend different outcomes with neoadjuvant chemotherapy (NACT). SGC was active in MIBC, showing a response rate (downstaging to pT $<$ 2) of 54.3% in 46 patients (pts) in a phase 2 trial (NCT01222676, *Necchi et al, GU ASCO 2017*). We analyzed gene expression profiles (GEP) and copy number variations (CNV) of transurethral resections (TURB) from these pts.

Methods: We analyzed 25 pts, 18 responders (R) and 7 non-responders (NR). GEP and CNV profiles were generated using Affymetrix Clariom™ D and OncoScan™ assays. Samples were assigned to claudin-low (CL), basal (B) or luminal (L) subtypes according to the BASE47 and BCL40 signatures. Genes differentially expressed or amplified/deleted between NR and R were functionally analyzed using Ingenuity Pathway Analysis (IPA) and Gene Set Enrichment Analysis.

Results: Transcriptional subtypes were robustly assigned to 24/25 pts: 13 were classified as L, 10 CL and 1 B. A significant association between subtypes and therapeutic response was observed (p = 0.002), with all L samples falling in the R group while CL were split between R and NR (5 *vs* 5). To avoid confounding related to the subtype we restricted the comparison of R and NR to CL samples. Through the use of IPA we identified activation of an IRF7-driven transcriptional program (p = 3.88E-12) in NR samples. In the NR group we found a positive enrichment of gene sets related to mRNA processing, cell cycle and oxidative phosphorylation and a negative enrichment of defensins. In addition, 19 genes were both significantly overexpressed and amplified in NR whereas copy number gains on chromosome 17, 18 and 20 characterized R samples. Limitations include the unassessable role of S contribution to GC.

Conclusions: Altogether, the results indicate that L tumors are responsive to SGC. Comparisons between R and NR within the CL group outlined potential genomic predictors of response. Once validated, pt selection criteria for NACT may be substantially improved. Comparison with profiling of response to NA pembrolizumab will be shown (NCT02736266).

Legal entity responsible for the study: Fondazione IRCCS Istituto Nazionale dei Tumori

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872P Outcomes based on plasma biomarkers in METEOR, a randomized phase 3 trial of cabozantinib (c) vs everolimus (e) in advanced renal cell carcinoma (rcc)

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Background: C inhibits tyrosine kinases that promote oncogenesis and resistance to antiangiogenic therapy in RCC, including MET, AXL, and VEGF receptors. In the phase 3 METEOR trial (NCT01865747), C significantly improved progression-free survival (PFS), overall survival (OS), and objective response rate (ORR) vs E in patients (pts) with advanced RCC after prior VEGFR-targeted therapy (Choueiri, Lancet Oncol 2016). The current study evaluated outcomes based on plasma biomarker levels.

Methods: Plasma samples collected at baseline and during treatment from 621 of 658 randomized pts were analyzed for HGF, MET, Gas6, AXL, VEGF, VEGFR2, CA9, and IL-8 by ELISA (Assay Gate, Ijamsville, MD). PFS and OS were analyzed based on low vs high ($<$ median vs $\geq$ median) biomarker levels at baseline.

Results: Analyses of PFS and OS based on baseline biomarker levels showed improvement with C vs E (hazard ratio $<$1) for all analyses of both low and high levels. PFS improvement for C vs E was most pronounced for low baseline levels of AXL and VEGF, while OS improvement for C vs E was most pronounced for low baseline levels of HGF, Gas6, AXL, and VEGF (Table). For a subset of biomarkers, medians for PFS and OS were longer for low baseline levels vs high for both treatment arms. Differences in OS medians for low vs high levels were largest for HGF (not reached [NR] vs 15.4 mo for C; 19.4 mo vs 13.0 mo for E), Gas6 (NR vs 17.2 mo for C; 18.4 mo vs 13.9 mo for E), VEGF (NR vs 16.1 mo for C; 18.4 mo vs 14.9 mo for E), and IL-8 (NR vs 17.2 mo for C; 19.4 mo vs 13.0 mo for E).

Table: 872P

Plasma Biomarker	C vs E, Hazard Ratio (95% CI) for OS	
	Low Biomarker	High Biomarker
HGF	0.48 (0.32, 0.70)	0.74 (0.56, 0.99)
MET	0.67 (0.48, 0.94)	0.62 (0.46, 0.84)
Gas6	0.53 (0.37, 0.75)	0.76 (0.56, 1.02)
AXL	0.54 (0.38, 0.76)	0.78 (0.58, 1.06)
VEGF	0.51 (0.36, 0.74)	0.78 (0.58, 1.04)
VEGFR2	0.63 (0.46, 0.86)	0.68 (0.49, 0.94)
IL-8	0.62 (0.43, 0.88)	0.69 (0.51, 0.93)

Conclusions: PFS and OS improved with C irrespective of baseline plasma biomarker levels in previously treated pts with advanced RCC vs E. However, low baseline levels of a subset of biomarkers were associated with better clinical outcomes with C.

Clinical trial identification: NCT01865747

Legal entity responsible for the study: Exelixis, Inc.

Funding: Exelixis, Inc.

Disclosure: T. Powles: Consultant/advisory: Exelexis Novartis GSK; Research funding: Exelexis Novartis GSK Genetech. R.J. Motzer: Consulting Role: Exelixis, Eisai, Pfizer, Novartis; Research Funding (institution): Exelixis, Eisai, Bristol-Myers Squib, Pfizer, Novartis. D.J. George: Ad Board: Bristol-Myers Squib, Exelixis, Genentech/Roche, Novartis, Pfizer; Corporate-sponsored Research: Bristol-Myers Squib, Exelixis, Genentech/Roche, Novartis, Pfizer Other: Acceleron – IDMC. E. Jonasch: Research funding: Exelixis, Pfizer, Novartis; Honoraria: Bristol-Myers Squib, Eisai, Exelixis, Novartis, Pfizer. S. Pal: Honoraria: Novartis, Medivation and Astellas Pharma; Consulting fees: Pfizer, Novartis, Aveo, Genentech, Exelixis, Bristol-Myers Squib, Astellas and GSK. N.M. Tannir: Ad Board: Bristol-Myers Squib, Exelixis, Nektar, Novartis, Pfizer, Argos, Calithera; Corproate-sponsored Research: Bristol-Myers Squib, Exelixis, Epizyme, Novartis, Miranti. S. Signoretti: Consulting Role: AstraZeneca, Merck; Research Funding (institution): AstraZeneca, Exelixis Patents/Intellectual Property: Biogenex. C. Scheffold: Employee: Exelixis. E. Wang, D.T. Aftab: Employee: Exelixis, Inc. B. Escudier: Honorarium: Bristol-Myers Squib, Novartis,

Pfizer, Ipsen, Roche, Bayer, Calithera, Acceleron, EUSA, Eisai. T.K. Choueiri: Research Funding: Pfizer, GSK, Novartis, Bristol-Myers Squib, Merck, Exelixis, Roche, AstraZeneca, Tracon, Peloton; Consulting Role: Pfizer, GSK, Novartis, Merck, Bayer, Eisai, Roche, Prometheus Labs Inc, Bristol-Myers Squib, Foundation Medicine Inc. All other authors have declared no conflicts of interest.

873P RX-3117, an oral hypomethylating agent to treat advanced solid tumors (st): Interim results from an ongoing phase 2a study in advanced urothelial cancer

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Background: RX-3117 is an oral small-molecule hypomethylating agent, cyclopentyl pyrimidyl nucleoside that is activated by uridine cytidine kinase 2. RX-3117 shows efficacy in various xenograft models, including those of gemcitabine resistant bladder and colorectal cancers. Data from the stage 1 of a Phase 2a clinical study of RX-3117 as a single agent in subjects with advanced urothelial cancer are described below.

Methods: This Phase 2a study with a 2-stage design (NCT02030067) evaluates the efficacy of RX-3117 in eligible subjects (aged $\geq$ 18 years) with advanced urothelial cancer previously treated with an unlimited number of prior therapies. Primary objectives include safety and efficacy of the recommended Phase 2 dose (RP2D) and schedule identified in the Phase 1 portion of the study. Subjects received 700 mg of oral RX-3117 daily for 3 weeks with 1 week of rest in each 4-week cycle. The response criteria of complete response or partial response in 1 or more subjects or stable disease for 4 cycles in 2 or more subjects in Stage 1 in order to proceed to Stage 2.

Results: As of May 2017, 10 subjects with advanced urothelial cancer were treated with RX-3117 (4 females, 6 males). Of those 10 subjects, 70% received $\geq$ 3 prior therapies, had performance score of 0-1 and multiple disease sites (lung, liver, lymph nodes and pelvis). Two subjects met the protocol defined response criteria of stable disease for 4 cycles of RX-3117 treatment; one subject received treatment for 168 days and another subject continues receiving therapy (147 days at abstract submission). In addition, 1 subject showed tumor shrinkage as measured by RECIST (-15%); another subject still on treatment showed a 19% tumor reduction after 2 cycles of RX-3117. Related adverse events were G2 anemia, G1 anorexia, G1 epistaxis, G1 fatigue, G1 nausea, G1 diarrhea, G1/G2 vomiting, G2 mucositis, G3 leukopenia, G1/G3 neutropenia, and G3 thrombocytopenia. One subject had a treatment delay and dose reduction.

Conclusions: Single agent RX-3117 appears to be safe and well tolerated and shows evidence of preliminary tumor activity. The predefined efficacy criteria was met in Stage 1, and Stage 2 is ongoing. Results from Stage 1 of the phase 2a will be presented.

Clinical trial identification: NCT02030067

Legal entity responsible for the study: Rexahn Pharmaceuticals, Inc

Funding: Rexahn Pharmaceuticals, Inc

Disclosure: J. Poore, C. Peterson, E. Benaim: Employee of Rexahn Pharmaceuticals, Inc. All other authors have declared no conflicts of interest.

874P Immune correlates for the efficacy of PEGylated Human IL-10 (AM0010) with nivolumab in renal cell cancer

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Background: At therapeutic concentrations AM0010 stimulates the cytotoxicity, survival and proliferation of CD8 T cells. IL-10 receptors and PD-1 are expressed on activated and exhausted CD8 T cells, providing a rationale for combining AM0010 and an anti-PD-1. AM0010 alone had partial tumor responses (PR) in 4 of 16 pts with poor to intermediate risk RCC. In dose escalation, 4 of 8 RCC patients receiving AM0010 plus pembrolizumab in 3rd line, had a PR. The mPFS was 16.7 months.

Methods: 29 pts with metastatic RCC were enrolled on AM0010 (10 or 20 ug/kg daily SC) and nivolumab (3mg/kg, q2wk IV). Two had favorable, 20 had intermediate and 4 had poor IMDC risk (3 data not available). Pts. had a median of 1 prior therapy (range 1-3), and at least one VEGFR-TKI. Tumor responses were assessed following irRC. Immune related cytokines in the serum, activation of blood derived T cells and clonal identity of peripheral T cell were measured.

Results: AMO010 plus nivolumab or pembrolizumab was well tolerated. TrAEs were reversible and transient. 14 patients on 20ug/kg AM0010 daily SC and nivolumab had at least 1 G3/4 TrAE, including anemia (10), thrombocytopenia (5), hypertriglyceridemia (5). Two pts had a reversible cytokine release syndrome with splenomegaly and increased immune mediated red blood cell phagocytosis most likely precipitated by T-cell activation, as both pts had objective tumor responses. Patients treated with 10ug/kg AM0010 and anti-PD-1 did not have hematologic G3/4 TrAEs. As of May 1 2017, PRs were observed in 9 of 26 evaluable pts (35%). An additional 12 pts have stable disease (46%), 7 of those have a tumor reduction $>$ 30% (in progress). The mPFS and mOS has not been reached, the mFU is 7.7 months (range 0.5-13.7). AM0010 + anti-PD1 increased Th1 cytokines in the serum, proliferation of PD1+ Lag3+ CD8 T cells and oligoclonal expansion of novel T cell clones in the blood. The expansion of invigorated T cells and the clonal expansion correlated with tumor responses.

Conclusions: AM0010 in combination with anti-PD-1 is well-tolerated in RCC pts, the recommended phase 2 dose is 10ug/kg. The efficacy and the observed CD8 T cell activation is promising and encourages the continued study of AM0010 in combination with nivolumab.

Clinical trial identification: NCT02009449

Legal entity responsible for the study: ARMO BioSciences

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875P Outcomes of patients with metastatic urothelial carcinoma (mUC) with exclusive bone metastases: Focus on a special patient population

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Background: Patients (pts) with aUC with exclusive bone metastatic spread represent a rare subgroup of pts with unique clinical features. These pts deserve special consideration, as they are usually excluded from clinical trials due to the lack of measurable disease according to RECIST criteria. We focused on their access to treatment and outcomes in a retrospective study.

Methods: Cases were extracted from the pool of 1,911 pts with a diagnosis of mUC from the RISC database (db). Data from 23 centers was collected. Results of 1st-line, platinum-based chemotherapy in bone-only pts were compared with those from the remaining pts in the RISC db. Summary statistics were used to describe pt characteristics and outcomes. Kaplan-Meier method was used to estimate time to event outcomes such as progression-free survival (PFS) and overall survival (OS). Both OS and PFS are measured from the date of diagnosis of metastatic disease. Univariable and multivariable Cox analyses were performed. All tests were two-sided and statistical significance was defined as a p-value $\leq$0.05.

Results: A total of 128 evaluable pts (6.7%), treated between 02/1997 and 04/2013, were identified. ECOG-PS was $\geq$1 in 85.9% vs. 66.3% of the remaining pts from RISC db. 73 (57%) received 1st-line chemotherapy, that was platinum-based in all pts, and 28 of them (38.4%) 2nd-line CT (vs. 75.8% and 42.5%, respectively, from the RISC db). On multivariable analyses, only the chemotherapy administration was significantly associated with improved OS among bone-only mUC pts ($p < 0.001$). Among platinum-treated pts (total evaluable N = 972), significantly-different PFS and OS estimates were observed according to the bone metastases status (no bone metastases vs. bone metastases only vs. bone + other, $p < 0.001$). 2-year PFS was: 37.4%, 28.8%, 25.9%. 2-year OS was: 35.5%, 15.8%, 23.0%, among the above subgroups, respectively.

Conclusions: Pts with bone only metastases are less likely to receive systemic therapy than pts with metastases to other sites, likely due to lower PS. The prognostic impact of having exclusive bone metastases or additional sites seems to be equally poor. Clinical trials with new agents should focus on this population.

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Funding: None
Disclosure: All authors have declared no conflicts of interest.

876P Efficacy of cabozantinib (C) after PD-1/PD-L1 checkpoint inhibitors in metastatic renal cell carcinoma (mRCC): The Gustave Roussy experience

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Background: Optimal treatment sequence in mRCC remains unclear, although PD-1/PD-L1 inhibitors are becoming standard of care in second or third-line. There is little evidence about the efficacy of antiangiogenic therapies after immune checkpoint inhibitors (ICI), especially of C, which was recently approved for mRCC. We report our initial experience of C efficacy after prior ICI.

Methods: We conducted a retrospective analysis of mRCC patients (pts) enrolled on clinical trials at Gustave Roussy with ICI with a special focus on C as subsequent therapy. Clinical outcome during C treatment, including Time to Treatment Failure (TTF), Objective Response Rate (ORR), Overall Survival (OS) and safety are reported.

Results: After a median follow-up of 60 months (mo), among 127 pts treated with ICI (n: 107; nivolumab), 44 (35%) were still on-treatment and 5 pts had stable disease after treatment interruption. Among the 78 pts who progressed after ICI, 22 pts (28%) never received further treatment. 56 pts (72%) received further therapies: 18 (32%) C, 25 (44%) Axitinib (A) and 13 (24%) other (O). C was given as third-line or beyond in 27% and 73% of pts, respectively. Before starting C, pts were only intermediate or poor prognosis by IMDC criteria. Considering all evaluable pts, ORR was 33%, median TTF was 7.99 mo and median OS was 12.33 mo. Focusing on C, ORR was 42% and no pts presented progressive disease as best response versus 37% for A with 2% progressive disease. Currently, median TTF and OS on C are not yet estimable (0.92-not reached); update on clinical outcome will be presented. Moreover, C demonstrated acceptable safety profile and the rate of treatment discontinuation because of adverse events was 11%.

Conclusions: In mRCC pts previously treated by ICI, treatment with C seems to be very active, irrespective of number of prior treatments or IMDC risk group. Prior PD-1/PD-L1 exposure did not influence safety of subsequent C therapy. Interestingly, activity of A also appears excellent, raising the hypothesis of enhanced efficacy of TKI after ICI.

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877P Second-line treatment patterns and outcomes of metastatic bladder cancer patients in clinical practice

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Background: There is no universally accepted standard therapy for second-line (2L) treatment of metastatic bladder cancer (mBC). We sought to evaluate treatment patterns and outcomes of patients (pts) receiving 2L treatment for mBC.

Methods: We identified pts receiving initial mBC treatment during an index period from January 2010-June 2014 by review of electronic health records (EHR) of McKesson Specialty Health/US Oncology, with follow-up through July 2016. Patients who subsequently received 2L therapy were included in this analysis. The Kaplan-Meier method was utilized to evaluate outcomes from 2L treatment initiation.

Results: Of 1155 pts receiving 1L treatment during the index period, 391 (33.9%) pts received 2L treatment and were eligible for analysis. The median age was 70 years (range 36-89) and 81.1% were men. Median time to initiation of 2L therapy following mBC diagnosis was 7.8 months(mos). 2L therapy was used in 33.6% of pts who received 1L cisplatin(cis)-based therapies and 34.0% of those who received other 1L therapies. 51.4% of 2L pts received combo-therapy; the common (>5% of total 2L utilization) regimens were carboplatin(carbo)/gemcitabine(gem) (14.8%), carbo/paclitaxel(pac) (12.0%), and cis/gem (7.7%). 48.6% of 2L pts received monotherapy; the common regimens were pac (17.4%), docetaxel (10.5%), pemetrexed (8.2%), and gem (6.6%). For the composite outcome of third-line therapy initiation or death, the median time-to-event for all 2L regimens was 5.2 mos (95% confidence interval [CI], 4.5 to 6.0). Median overall survival (OS) for all 2L regimens was 9.4 mos (95% CI, 8.2 to 11.1). Time-to-event outcomes were significantly different across the various regimens ($p = 0.0005$).

Conclusions: This real-world data provides important insights into patterns of care and outcomes for 2L mBC pts. These results concur with other observational studies in this time frame, suggesting that only one third of 1L mBC pts progress to 2L treatment. Taxane and platinum-based regimens predominated in the 2L, although patterns of treatment were consistent with prior research showing that no clear standard of care exists for these pts. Monotherapy and combination regimens are utilized in equal proportions, both producing poor outcomes for mBC pts.

Legal entity responsible for the study: Kyle Flannery et al. had final responsibility for conduct and reporting of this study.
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878P Comparing ITC results from lenvatinib plus everolimus for second-line treatment of advanced/metastatic renal cell carcinoma: Crossover versus no crossover

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Background: An indirect treatment comparison (ITC) involving lenvatinib plus everolimus (LEN+EVE) was conducted using networked data from HOPE 205, CHECKMATE-025, METEOR, AXIS, RECORD-1 and TARGET. The ITC incorporated adjustments for crossover to investigational treatment. Results showed superiority of LEN+EVE over EVE alone; and inferiority versus pazopanib (PAZ) or sunitinib (SUN) alone in overall survival (OS) for second-line treatment of advanced/metastatic renal cell carcinoma. No statistically significant differences in OS were found between LEN+EVE versus nivolumab (NIV), cabozantinib (CAB), axitinib (AXI), or placebo.

Methods: A subsequent analysis was conducted using intention to treat (ITT) to evaluate the impact of crossover correction on OS estimates and additionally to uncover any potential bias due to its absence. Three ITC scenarios were analyzed: A) all comparators plus placebo versus EVE; B) all comparators versus placebo; and C) LEN+EVE versus all comparators.

Results: Scenario "A" showed consistent variance in survival benefit for ITT versus crossover by an average of 20%. Hazard ratios for AXI versus EVE shifted from below null (0.98) to above null (1.27); and mortality risk (placebo vs. EVE) moved 51% further from null (1.15 vs. 1.67). ITT estimates for Scenarios "B" and "C" showed on average 9% and 14% differences in OS benefits, respectively, versus crossover. In Scenario "C", estimates for LEN+EVE versus PAZ or LEN+EVE versus SUN showed superiority with ITT data (0.82 or 0.75) but were inferior (1.2 or 1.09) with crossover.

Conclusions: Bias was observed in naive approaches to survival analysis in the presence of crossover. Failure to account for this in clinical trials may have implications on the comparative effectiveness profile and also on the cost-effectiveness results, and may lead to inconsistent resource allocation decisions.

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879P Urine-derived lymphocytes (UDLs) as a non-invasive surrogate marker of tumour infiltrating lymphocytes (TILs) in patients with muscle invasive bladder cancer (MIBC)

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Background: The therapeutic targeting of PD-1 and PD-L1 has led to durable responses in metastatic bladder cancer, yet the majority of patients (pts) fail to respond. Here, we characterised the immune phenotype and TCR repertoire in tumour and UDLs in patients with MIBC for the identification of potential T cell biomarkers of response and resistance to checkpoint blockade.

Methods: Matched bladder tumour, normal urothelium (NU), urine and peripheral blood mononuclear cells (PBMC) were collected from 30 pts undergoing cystectomy. Multi-parametric flow cytometry and immunohistochemistry were used to determine the abundance of $CD8^+$, $CD4^+FoxP3^-$ (CD4eff) and $CD4^+FoxP3^+$ (Treg) T cell subsets and co-inhibitory (PD-1, CTLA-4, TIM-3) and co-stimulatory (ICOS, 4-1BB) immune

checkpoint molecules. T cell receptor (TCR) repertoire was determined using quantitative high throughput sequencing of α and β TCR chains followed by Decombinator bioinformatics analysis.

Results: UDLs were identified in 19/24 (80%) of MIBC pts with tumour *in situ* compared to 3/6 (50%) pts with pathological downstaging (pT0) following neo-adjuvant therapy. Urine, tumour and PBMC specimens were found to have a similar CD8/Treg ratio that was significantly higher in NU. Co-stimulatory and co-inhibitory checkpoint molecules were similarly distributed across $CD8^+$, CD4eff and Treg within tumour, urine and NU compartments, however significantly different to PBMC, irrespective of prior treatment. Preliminary analysis revealed a higher degree of similarity between the TCR repertoires of urine and matched tumour as compared with urine and NU or urine and PBMC samples.

Conclusions: These data suggest that UDLs are an accessible source of T cells from pts with MIBC that accurately map the immune landscape of TILs. UDL analysis represents a liquid biopsy to inform clinically relevant immunological parameters, including the CD8/Treg ratio, target checkpoint expression and TCR repertoire, irrespective of prior treatment. Further translational studies are ongoing to evaluate whether UDL analysis may serve as a non-invasive, dynamic biomarker to predict immunotherapy outcome in MIBC.

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880P Biomarkers before and after nephrectomy of locally advanced or metastatic renal cell carcinoma (RCC) treated with everolimus: Neorad phase 2 trial (PREDICT consortium)

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Background: Although many drugs are available in RCC, we still lack predictive biomarkers of disease recurrence or progression for personalized treatment. NEORAD clinical trial (NCT01715935) was designed to evaluate biomarkers modulation by everolimus (Ev) prior to nephrectomy on several tissue and circulating cells.

Methods: French open-label, exploratory, single-arm, multicenter trial, part of PREDICT consortium. Population: locally-advanced (LA), metastatic (M) RCC. Endpoints: primary: objective clinical benefit (CR, PR, SD upon RECIST 1.1) after 6 weeks neoadjuvant Ev (10 mg daily) prior nephrectomy; secondary: PFS, OS, toxicity. Multi-region sequencing (biopsy and surgery specimens) explored mutational status of genes of interest. After nephrectomy, Ev was reintroduced in M pts until PD or end of 12m follow-up. Treatment was continued until PD or unacceptable toxicity.

Results: 25 pts accrued (44 screened) between 05/2012 and 07/2015: LA = 14, M = 11 underwent biopsy at screening for tissue sampling then further nephrectomy. Population (LA/M): clear-cell=13/10, papillary=1/1, median age(y): 60/63, sarcomatoid component: 3 M pts, ECOG-PS: 0=10/4, 1=4/7, extra-renal metastatic sites: bone, lung, nodes, adrenal. Change in renal tumor size between baseline and D42: 0%. In M, Ev was resumed for 8 pts after nephrectomy with 2 PR and 6 SD. PFS (mo): M = 3.1 [1.41; 12.2]. Median follow-up (mo): 17.4 [3.3; 43.2]. PFS at 12 months: LA = 78%, M = 18% Toxicity of Ev was as expected and no adverse event in terms of surgical procedure was observed. Pts with following gene mutations exhibited a poor PFS: SEDT2: HR = 2.54 (0.63 – 10.28), BAP1: HR = 3.19 (0.78 – 13.12), TSC2: HR = 2.37 (0.49 – 11.53); further correlations will be presented at ESMO meeting.

Conclusions: NEORAD was the 1st neoadjuvant study of Ev in RCC. Despite limited number of pts, we generated a large amount of longitudinal data including exome sequencing, circulating biomarkers, angiogenesis and immunity factors. All these data could help decipher mechanisms of resistance, evaluate predictive signatures or add further knowledge to mechanisms involved in mTOR pathways.

Clinical trial identification: NCT01715935

Legal entity responsible for the study: Stéphane Oudard, MD, PhD

Funding: PREDICT Consortium

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881P Predicted benefits of adjuvant sorafenib after nephrectomy for renal cell carcinoma (RCC) in SORCE: an international, placebo-controlled, randomised phase 3 trial

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Background: The effects on survival of adjuvant therapy with a VEGF-TKI after nephrectomy for RCC are uncertain. Survival rates, times and benefits were predicted by medical oncologists at baseline for each patient they recruited to SORCE.

Methods: Medical oncologists at 20 sites in ANZ and 12 in the UK answered the following questions at baseline for each patient they recruited: the predicted overall survival rate at 5 years (SR) and predicted overall survival time (ST) without adjuvant sorafenib; and, the predicted absolute improvements in SR and ST with 1 year of adjuvant sorafenib. We used Spearman's rank correlation (r_s) to assess associations, and Wilcoxon signed rank tests to assess differences between the paired SR–ST values. We assumed exponential survival distributions to calculate: (i) % alive at 5-yrs corresponding to ST estimates, and (ii) hazard ratios (HRs) corresponding to predicted benefits on overall survival. We hypothesized that these HRs should be less extreme (numerically larger) than the target HR of 0.75 for disease free survival used to design the trial.

Table: 881P

	ST[1] In Years	ST[1] Calculated % alive at 5-yrs [a]	SR[1] Estimated % alive at 5-yrs [b]	Difference[1] [a]-[b]	r_s [a] vs [b]
Survival without sorafenib	7	61	60	0 (-7 to 9)	0.62
	(5 to 12)	(50 to 75)	(50 to 70)	p = 0.6	p < .001
Improvement with sorafenib	1	6	7	−2 (-6 to 1)	0.53
	(1 to 5)	(3 to 10)	(5 to 15)	p < .0001	p < .001
Hazard Ratio	0.83	0.83	0.76	0.09 (-0.01 to 0.21)	0.41
	(0.67 to 0.91)	(0.67 to 0.91)	(0.62 to 0.82)	p < .0001	p < .0001

[1]Medians (IQRs)

Results: The table shows paired estimates of ST and SR from 61 medical oncologists for 176 of the 1711 SORCE patients. Predictions of survival without sorafenib were similar whether based on ST or SR. The predicted benefits of sorafenib based on SR were moderately correlated with those based on ST, but significantly larger. The proportion of HRs > 0.75 was 51% based on SRs vs 66% based on STs.

Conclusions: The predicted benefits of adjuvant sorafenib based on SRs were often larger than hypothesized, and larger than predictions based on ST, which were more consistent with the target HR. These data suggest that predictions of benefit in this setting may be more conservative and plausible when based on ST rather than SR.

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882P Potential impact of avelumab+axitinib (A+Ax) on tumor size (TS) compared with historical data of sunitinib (S) as evaluated by a modeling and simulation (MS) approach

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Background: Combining an immune checkpoint inhibitor (A) with a targeted VEGF antiangiogenic agent (Ax) may leverage complementary mechanisms of action for treatment of metastatic renal cell carcinoma (mRCC). JAVELIN Renal 100 is a phase (Ph) 1b trial evaluating the clinical activity and safety of A+Ax in treatment-naïve patients (pts) with mRCC. An early evaluation of the effect of A+Ax on TS, i.e. sum of diameters for target lesions, compared to historical S, the standard of care[1], can inform on decisions for future drug development for A+Ax. Claret et al. have shown that a greater early TS reduction at week 8 of treatment (TR8) is correlated with a longer progression free survival time in trials of 1st line treatment of mRCC[2]. The objective of this analysis is to apply MS methodology to data from JAVELIN Renal 100 to evaluate the potential effect of A+Ax on TS as compared to historical S data.

Methods: A tumor dynamic model[3] was applied to the longitudinal TS data obtained from the Ph1b study of A+Ax and from the historical Ph3 trial of S. The model includes 3 parameters representing the rate of tumor growth (KL), the rate of drug effect in reducing tumor size (KD), and the rate of the loss of drug effect (DM). The TR8 for each patient can be derived from the model. A larger KD, smaller DM, and TR8 suggested a greater effect. The parameters and TR8 from the two treatments are estimated and compared using ANOVA.

Results: The summaries of the model parameters, TR8, and p-value of ANOVA analysis are presented in the Table below:

Table: 882P

	Avelumab + axitinib (N = 53) (mean ± SD)	Sunitinib alone (N = 349) (mean ± SD)	p-value
TR8	0.757 ± 0.162	0.808 ± 0.132	0.012
KL (1/week)	0.011 ± 0.014	0.009 ± 0.012	0.398
KD (1/week)	0.065 ± 0.027	0.054 ± 0.034	0.021
DM (1/week)	0.081 ± 0.024	0.095 ± 0.049	0.040

A+Ax resulted in a greater effect on TR8, a faster tumor size reduction and a more sustained effect than S.

Conclusions: MS is an effective tool to inform drug development. These results suggest that A+Ax results in a greater TS reduction than S, supporting further investigation of A+Ax vs S in the JAVELIN 101 randomized Ph3 trial. References: 1. Motzer R *et al* NEJM (2007) 356:115 2. Claret L *et al* Cancer Chemother Pharmacol (2016) 78:605 3. Claret L *et al* PAGE 2012 Abstr 2328.

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Legal entity responsible for the study: Merck KGaA, Darmstadt, Germany; Pfizer Inc, New York, NY, USA.

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883P Synchronous vs metachronous metastatic disease: Impact of time to metastasis on outcome in metastatic renal cell carcinoma patients treated with targeted therapy

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Background: Patients (pts) with metastatic renal cell carcinoma (mRCC) may present with primary metastases (synchronous disease) or develop metastases during follow-up (metachronous disease). The impact of timing of metastatic disease outbreak on outcomes from targeted therapy (TKI) is unclear.

Methods: We used the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) to assess overall survival (OS) and time to treatment failure (TTF) on first line TKI, and performed Cox regression analyses comparing synchronous (metastases ≤ 3 mo of initial diagnosis of cancer) vs metachronous disease (metastasis diagnosed post initial diagnosis, evaluated by intervals >3-12 mo, >1-2 yrs, >2-7 yrs, and >7yrs).

Results: In 7386 pts with mRCC treated with first line TKI, 3906 pts (53%) had synchronous and 3480 pts (47%) had metachronous metastases. Synchronous *vs* metachronous disease by intervals >3-12 mo, >1-2 yrs, >2-7 yrs, >7yrs correlated with lower age at TKI initiation (mean 61 yrs vs 61, 62, 63, 66 yrs, respectively, $p < 0.0001$), higher rate of non-clear cell histology (14% vs 12%, 10%, 10%, 7%, respectively, $p < 0.0001$), and higher rate of IMDC risk features (mean 2.3 vs 1.6, 0.9, 0.9, 0.8, $p < 0.0001$). Compared with synchronous disease, the longer time to metastases was significantly associated with improved OS and TTF from TKI therapy initiation in multivariable Cox regression, adjusted for nephrectomy status, histology (cc vs ncc), IMDC risk factors (Hgb, Corrected calcium, Neutrophil, platelets, Karnofsky performance status), number of metastasis (1 vs > 1), age at TKI initiation and year of TKI initiation (2003-2007, 2008-2012, 2013-2016).

Conclusions: Timing of metastases post initial RCC diagnosis impacts outcome with targeted therapy in mRCC. This may need to be taken into consideration in clinical trial designs.

Legal entity responsible for the study: The International Metastatic Renal Cell Carcinoma Database Consortium (IMDC)

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Table: 883P Association of time to metastases with OS and TTF from TKI initiation

	OS					TTF				
time to metastases	**Total**	**Failed**	**Median, months 95%CI**	**Adjusted Hazard ratio (95%CI)**	**Adjusted P-value**	**Total**	**Failed**	**Median, months 95%CI**	**Adjusted Hazard ratio (95%CI)**	**Adjusted P-value**
0-3mo	3906(53%)	2852	16.7(15.9-17.5)	1.00(reference)	–	3880	3483	5.6(5.5-5.8)	1.00(reference)	–
>3∼12mo	1055(14%)	726	23.8(21.6-26.1)	1.06(0.98-1.16)	0.162	1050	941	7.3(6.6-8.0)	1.02(0.95-1.100	0.551
>1∼2yrs	638(9%)	401	30.2(26.7-32.5)	**0.84(0.76-0.94)**	0.002	635	564	8.0(7.3-8.9)	0.99(0.90-1.08)	0.767
>2∼7yrs	1155(16%)	729	34.8(32.4-38.1)	**0.76(0.70-0.83)**	<.0001	1151	1011	10.8(9.6-11.5)	**0.83(0.77-0.89)**	<.0001
>7yrs	632(9%)	359	41.7(36.3-46.0)	**0.65(0.58-0.73)**	<.0001	627	527	13.3(11.5-14.9)	**0.67(0.61-0.74)**	<.0001
Total	7386(100%)	5067				7343	6526			

Janssen. T.K. Choueiri: Consulting or advisory role for Bayer, Bristol-Myers Squib (institutional), GSK, Merck, Novartis, and Pfizer; and institutional research funding from AstraZeneca, Bristol-Myers Squib, Exelixis, GSK, Merck, Novartis, Peloton Therapeutics, Pfizer, Roche/Genentech, and TRACON Pharma. D.Y.C. Heng: Advisory boards Pfizer, Novartis, Bristol-Myers Squib, Exilexis. All other authors have declared no conflicts of interest.

884P SPAZO2 (SOGUG): Comparative effectiveness of pazopanib in metastatic renal carcinoma (mRC): Ineligible (I) vs eligible (E) patients for clinical trials

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Background: Ineligibility for clinical trials (CT) may be an unfavorable prognostic factor in mRC. There is no information about the effectiveness of pazopanib in patients (pt) ineligible for CT. We aimed to assess the effect of ineligibility in outcomes in mRC, and the effectiveness of pazopanib in this setting.

Methods: SPAZO2 (NCT03091465) was a retrospective real-world study to analyze the effectiveness of 1st-line pazopanib and subsequent therapies in mRC in several settings. Data from 530 pt treated with frontline pazopanib outside CT in 50 centers in Spain were collected, and externally monitored. Ineligibility criteria: ECOG >1, pure nonclear-cell, brain metastases, Hgb < =9 g/dl, renal failure, severe ischemic disease, age >80 y, stroke, chronic liver disease, or recent neoplasia.

Results: A total of 217 pt (40.9%) fulfilled criteria for ineligibility. There were significant differences (I vs E) in age >75 (39% vs 15%), nephrectomy (61% vs 78%), IMDC (favorable: 8.8% vs 17.9%, intermediate: 50.2% vs 68.4%, poor: 41% vs 13.7%), metastases (lymph nodes: 51% vs 41%, lung: 65% vs 72%, liver: 21% vs 15%, bone: 31% vs 22%, skin/soft-tissue: 30% vs 16%, and CNS (13% vs 0%) but no in sex (68% vs 67% males). Discontinuation due to toxicity or comorbidities was 19% vs 17%. There were also differences ($p < 0.05$) in 2nd-lines (53% vs 61%), response, PFS and OS (Table). Median follow-up was 39 mo. Median PFS and OS were 9.8 and 19.6 mo respectively. After adjusting by IMDC and age (Cox regression), ineligibility was significantly associated with a higher risk of progression (HR: 1.4 95%IC: 1.1 - 1.7) and death (HR: 1.5 95%IC: 1.2 - 1.9). Only anemia and asthenia (all grades) were significantly higher in the I group.

Conclusions: In our series, "real world eligible pt" had similar outcome to the obtained in clinical trials. On the contrary, "real world ineligible pt" for clinical trials had significantly lower response rate, and shorter PFS and OS than elegible pt. Pazopanib was safe and effective in both subpopulations of patients.

Clinical trial identification: NCT03091465

Legal entity responsible for the study: SOGUG

Funding: Novartis

Disclosure: J. Arranz Arija: Grant for research from Novartis. Participation in advisory boards for Novartis and Pfizer. B. Pérez Valderrama: Consulting/Advisory role for Astellas Pharma, Novartis, Pfizer, Pierre Fabre, Bayer, Sanofi, Bristol-Myers Squib and Roche. J.P. Maroto Rey: Advisory Board for Novartis, Pfizer, Ibsen and Bristol. M.A. Climent Duran: Pfizer and Novartis talks, advisory role for Pfizer. All other authors have declared no conflicts of interest.

Table: 884P

	Overall			IMDC prognostic subgroups					
	N = 530	N = 217	N = 313	Favourable (14.2%)		Intermediate (60.9%)		Poor (24.9%)	
	All	I	E	I	E	I	E	I	E
CR	4.4%	1%	7%	5%	11%	1%	6%	0%	5%
PR	28.5%	23%	33%	42%	52%	24%	28%	16%	28%
SD	37.3%	42%	34%	32%	33%	51%	36%	33%	25%
Median PFS*	9.8 (9-11)	7.7 (6-9)	11.5 (9-14)	13.5 (3-24)	23.5 (15-32)	9.7 (7-12)	10.5 (8-13)	5.2 (3-8)	7.5 (4-11)
Median OS*	19.6 (17-22)	12.8 (10-16)	24.4 (20-28)	29 (26-32)	42.3 (33-52)	19.1 (14-25)	21.5 (19-24)	5.9 (3-9)	14.2 (3-26)

*Months (IC95%); I: ineligible; E: eligible.

885P Sunitinib versus pazopanib for patients with metastatic renal cell carcinoma: Two Turkish hospital experience, a retrospective comparative case series study

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Background: Pazopanib (PAZ) and Sunitinib (SUN), are two oral multikinase angiogenesis inhibitors which are prescribed frequently. However, the outcomes in real world of Turkish population have not extensively been studied.

Methods: Patients assessed retrospectively at two Turkish hospitals between 2006 and 2016.

Results: Median age of patients was 60 (28-87) years and 70% of patients were male. ECOG performance score was 0 and 1 in 73% of patients. Twelve patients (15%) had non-clear cell carcinoma histology. Pathological characteristics, MSKCC risk groups, median follow up, response rates and survival are shown in Table. In the SUN group, the patients had more grade 3-4 adverse events (Table).

Table: 885P Patient characteristics, responses to treatment, survival, and adverse events

	Sunitinib (n = 41)	Pazopanib (n = 38)	p value
MSKCC risk group	Favorable 31% Intermediate 56% Poor 12.5%	Favorable 31% Intermediate 47% Poor 21%	p = 0.66
T3-T4 stage	49%	47%	p = 0.38
Node positivity (%)	20%	8%	p = 0.10
Local recurrence (%)	20%	30%	p = 0.36
Median follow-up	18 months	13 months	p = 0.21
ORR	34%	37%	p = 0.96
DCR	78%	87%	p = 0.046
Progression	73% (n = 30)	50% (n = 19)	p = 0.08
Median PFS	8months	8months	p = 0.49
Median OS	22 months	21 months	p = 0.21
Fatigue, all grades	45%	74%	p = 0.48
Skin changes, all grades	44%	44%	p = 0.24
Anemia, all grades	35%	42%	p = 0.75
Grade 3-4 adverse events	59%	16%	p < 0.001
Dose reduction	50%	24%	p = 0.021
Treatment cessation	37%	26%	p = 0.37

Conclusions: In our study, there was no difference in terms of survival between two agents. However, patients treated with SUN had more grade 3-4 adverse effects which prompted dose reduction and cessation.

Legal entity responsible for the study: Individuals, Meltem Ekenel and Senem Karabulut

Funding: None

Disclosure: All authors have declared no conflicts of interest.

886P SPAZO2 (SOGUG): Comparative effectiveness of everolimus (Ev) vs axitinib (Ax) as second-line after first-line pazopanib (1stPz) in metastatic renal carcinoma (mRC)

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Background: Pivotal studies of axitinib and everolimus in 2nd-line mRC did not include pt treated with 1stPz. In addition, E vs A have not been directly compared in clinical trials in this setting. We aimed to compare the effectiveness of E vs A in real life, as second-line after pazopanib in mRC.

Methods: SPAZO2 (NCT03091465) was a retrospective real-world study to analyze the effectiveness of 1stPz and subsequent therapies in mRC in several settings in every day practice. Data from 530 pt treated with frontline pazopanib outside CT in 50 centers in Spain were collected by investigators, but monitored and entered in a database by an external CRO.

Results: Out of 285 pt receiving 2nd-line targeted therapies after 1stPz, 189 received either Ax (88, 46.6%) or Ev (101, 53.4%). There were no significant differences (Ax vs Ev), in age (63 y vs 66 y), sex (68% vs 64% males), nephrectomy (76% vs 67%), metastases in lymph nodes (58% vs 52%), liver (21% vs 28%), bone (45% vs 41%), CNS (6%), adrenal (4% vs 5%), pleura/peritoneum (4% vs 6%), or pancreas (4% vs 6%), but there were in age >75 (14% vs 25%), nonclear cell component (1 vs 16%), and lung (85 vs 72%) and skin/soft-tissue (20 vs 28%) metastases. According to the IMDC for 2nd-line targeted therapies, 17% vs 9% of pt were in the favorable risk group, 65% vs 69% in the intermediate risk, and 18% vs 22% in the poor risk. All-grades hypertension (32.6% vs 3.6%) and hypothyroidism (16% vs 6%) were significantly higher with Ax, whereas anemia (21.4% vs 55%), and mucositis (12.3% vs 39%) were more frequent with Ev. Subsequent therapies were given in 56% in Ax vs 46% in Eve. After median follow-up of 28 mo, 74.6 of pt have died. Outcomes and 95%CI are summarized in the table.

Table: 886P

	Response		PFS		OS	
	ORR	SD	Median	6 monts	Median	1 year
Axitinib	13.1%	42.9%	5.3 (3-7)	47%	11.6 (7-16)	49%
Everolimus	9.3%	43%	4.6 (3-6)	39%	9.5 (7-12)	43%
Overall	11.2%	42.9%	5.0 (4-6)	43%	10.7 (8-13)	46%
	p ns		HR*: 0.76 (0.5-1.1)		HR*: 0.81 (0.6-1.2)	

*Adjusted by IMDC, metastases, age, histology and subsequent therapies.

Conclusions: In this real world study in pt with mRC, we could not find statistically significant differences in effectiveness between axitinib and everolimus as 2nd-line after 1st line pazopanib. These results validate the use of both drugs in terms of clinical benefit, PFS and OS.

Clinical trial identification: NCT03091465

Legal entity responsible for the study: SOGUG

Funding: Novartis

Disclosure: J. Arranz Arija: AdBo from Novartis and Pfizer. B. Pérez-Valderrama: Consulting/Advisory role for Astellas Pharma, Novartis, Pfizer, Pierre Fabre, Bayer, Sanofi, Bristol-Myers Squib and Roche. J. Puertas Alvarez: Participation in advisory board meetings from Pfizer, Astellas, Novartis, Sanofi, GlaxoSmithKline, AstraZeneca, Pharmamar, Hospira, Janssen, Eisai, Roche, Lilly, and Bayer. All other authors have declared no conflicts of interest.

Table: 887P

	Age, median (range)	Brain Mets	Liver Mets	Bone Mets
	Male %	65 (43-77) 72	65 (43-81) 70	65 (40-84) 79
ECOG PS %:	**0 1 2 NA**	41 50 6 3	42 50 7 1	39 48 10 3
Number of prior Therapies %:	**1 2 3 > =4 NA**	13 44 37 6 0	13 37 24 24 2	14 36 30 19 1

887P Negative prognostic factors and resulting clinical outcome in patients (pts) with metastatic renal cell carcinoma (mRCC) included in the Italian nivolumab expanded access program (EAP)

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Background: In recent years, prognostic classifications have been considered an area of growing interest in mRCC. However, independently from the classification used (Memorial Sloan Kettering versus Heng's) the presence of brain, liver and bone metastases (mets) or sarcomatoid features (G4) resulted in a poorer outcome for pts with mRCC treated with targeted therapies (antiangiogenic agents or mTOR Inhibitors). Regarding this topic, the large Italian EAP represent an important opportunity to analyze the impact of nivolumab in pts treated in a daily clinical practice setting.

Methods: Nivolumab was available upon physician request for pts aged ≥18 years who relapsed after at least one prior systemic treatment in the advanced or metastatic setting. Nivolumab 3 mg/kg was administered intravenously every 2 weeks for a maximum of 24 months. Pts included in the analysis had received ≥ 1 dose of nivolumab and were monitored for adverse events (AEs) using Common Terminology Criteria for Adverse Events.

Results: Of 389 Italian pts with mRCC enrolled in the EAP, 32 pts (8%) had brain mets, 128 (33%) had liver and 193 (50%) had bone mets. Baseline characteristic are described in the Table. These pts achieved a disease control rate (DCR) of 53%, 45% and 47% respectively. Six and 12 months overall survival rates in the 3 groups of mets were 87.0% and 66.8%, 75.6% and 62.0%, 78.0% and 58.9%, respectively. Histological grading, a matter of high interest, was assigned according to Fuhrman's classification: 51 pts had G4 tumor. The objective response rates in these pts and in the overall population were 23% and 22%, respectively, with a 6 and 12 months OS rate of 61% and 53.6% for the G4 group. The safety profile of the subgroups described above was in line with the general population.

Conclusions: These results suggest that also pts with poor prognostic factors may derive relevant benefits with nivolumab, with safety results consistent with previously reported data.

Clinical trial identification: Expanded Access Program

Legal entity responsible for the study: Italian RCC EAP Group

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Disclosure: S. Bracarda: Advisory Board Member for Pfizer, Novartis, Bristol-Myers Squib, Exelixis, Ipsen, Roche, Genentech, Eusa Pharma. PI for clinical studies with Bristol-Myers Squib, Pfizer, Roche, Exelixis. L. Galli: Advisory Board for Pfizer, Novartis. U. De Giorgi: Advisory Board for Bristol-Myers Squib, Pfizer, Novartis, Ipsen, Astellas, Janssen, Sanofi. G. Procopio, C. Porta: Advisory Board for Bristol-Myers Squib, Pfizer, Novartis, Ipsen. E. Cortesi: Advisory Board for Bristol-Myers Squib, Pfizer, Ipsen. All other authors have declared no conflicts of interest.

888P Change in neutrophil-to-lymphocyte ratio (NLR) in response to immunotherapy for metastatic renal cell carcinoma (mRCC)

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Background: Elevated NLR is associated with worse outcomes in several malignancies, including mRCC. However, its role in the current immunotherapy era is unknown. We investigated the utility of NLR at baseline and during therapy in mRCC patients treated with PD-1/PD-L1 immunotherapy (IO).

Methods: 116 patients from Dana-Farber Cancer Institute (Boston, MA) receiving IO-based therapies were included. NLR was examined at baseline and 6 (±2) weeks later. Landmark analysis at 6 weeks was conducted to explore the prognostic value of relative NLR change on overall survival (OS), progression-free survival (PFS), and objective response rate (ORR) using Cox or logistic regression models, adjusted for line of therapy, number of IMDC risk factors, histology and baseline NLR.

Results: Median follow up was 16.3 months (range: 1.4-64.2). Median duration on therapy was 7 months (<1-58.6). IMDC risk groups were: 21% favorable, 56% intermediate, 22% poor-risk. 43% were on first-line IO and 57% on 2nd line or more. Median NLR was 3.7 (1.3-16.1) at baseline and 3.9 (1.1-49.6) at week 6. Higher NLR at baseline and at 6-weeks showed a trend to reduced ORR and worse PFS and OS, and NLR at 6-weeks was a stronger prognostic than baseline values (Table). Compared with no change from baseline, increase in NLR by ≥ 25% at 6-weeks was associated with reduced ORR and significantly worse PFS and OS in multivariate analysis, whereas a decrease in NLR by ≥ 25% was associated with improved outcomes.

Conclusions: Early decline and NLR at 6-weeks are associated with significantly improved outcomes in mRCC patients treated with IO, whereas an increase is associated

Table: 888P

		ORR(CR+PR)		PFS		OS	
	N	Adjusted-OR	p-value	Adjusted-HR	p-value	Adjusted-HR	p-value
Continuous Ln(NLR) Baseline**	116	0.58 (0.23-1.42)	0.232	1.36 (0.78-2.37)	0.269	1.74 (0.82-3.69)	0.147
Continuous Ln(NLR) 6-weeks**	113	0.28 (0.11-0.69)	**0.006**	2.39 (1.38-4.15)	**0.002**	3.24 (1.83-5.74)	**<0.001**
NLR-change 6-weeks			0.357		**0.003**		**0.008**
Decrease ≥25%	22	1.63 (0.47-5.60)		0.67 (0.31-1.46)		0.25 (0.08-0.77)	
No change	55	1.00 (ref)		1.00 (ref)		1.00 (ref)	
Increase ≥25%	36	0.61 (0.22-1.66)		2.30 (1.30-4.07)		1.50 (0.71-3.16)	

**Natural log-transformed

with worse outcomes. The prognostic value of the readily-available NLR warrants larger, prospective validation.

Legal entity responsible for the study: Dana-Farber/Harvard Cancer Center

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889P Broad immunomodulating effect of first-line pazopanib in metastatic renal cell carcinoma patients

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Background: The impact of tyrosine kinase inhibitors (TKIs) on tumor immunity of patients (pts) with metastatic renal cell carcinoma (mRCC) is largely unknown. We investigated the activity of pazopanib in counteracting tumor-induced immunosuppression and boosting adaptive immune response.

Methods: Sixteen mRCC pts receiving first-line pazopanib were prospectively analyzed at baseline, 3 and 6 months for blood Immune profiling by multicolor cytofluorimetry. Gene expression analysis was performed by Illumina HT12v4 BeadChip Arrays. Data were evaluated by t-test, enrichment analysis and deconvolution algorithms.

Results: Pazopanib administration (800 mg per os/daily) was associated with a significant decrease of cell subsets involved in immunosuppression, including $CD14^+$ monocytes, monocytic $CD14^+$ $HLA\text{-}DR^{neg}$ myeloid derived suppressor cells (MDSC) and $CD14^+PDL\text{-}1^+$ cells. Similarly, low density $CD15^+$ granulocytic MDSC and $CD4^+$ $CD25^{high}$ $Foxp3^+$ regulatory T cells were reduced by treatment. Concomitantly, a boost of antitumor effectors, such as activated T lymphocytes (identified as $CD3^+PD\text{-}1^{dim}$ T cells) and cytotoxic $CD3^-CD16^+CD56^{dim}$ NK cells, was observed. Changes were more evident at 3 months and in pts achieving clinical benefit (69%), defined as the sum of partial response and stable disease at first restaging. Interestingly, a statistically significant increase of lymphocyte/monocyte ratio, as determined by routine blood test was also detected. Gene expression analysis confirmed the immunoregulatory effects of pazopanib. By comparing with those collected after 3 months after treatment start and pre-treatment samples, pathway-enrichment analysis revealed a coherent modulation of NK Granzyme A, IL8 signaling and other immune-related pathways. Similarly, using deconvolution algorithms, we observed an enrichment of NK and CD8+ T cell transcripts.

Conclusions: Pazopanib reshapes tumor immunity by reducing immunosuppressive cells (MDSC and Treg) and triggering T cells and NK effectors. These data provide a strong rationale for using Pazopanib both before an immunochecpoints inhibitors and also in combination strategies based on the synergism between TKIs and immunotherapy.

Legal entity responsible for the study: Fondazione IRCCS Istituto Nazionale dei Tumori of Milan

Funding: None

Disclosure: E. Verzoni: Reports receiving fees for serving on advisory boards from Pfizer and Novartis. All other authors have declared no conflicts of interest.

890P Prospective comparison of RECIST and alternative response assessment criteria in the evaluation of metastatic renal cell cancer patients from phase II of the multi-centre randomised STAR trial

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Background: Combined size and enhancement criteria show potential to predict earlier disease response or progression in metastatic renal cancer (mRCC). We assessed categorisation differences using RECIST 1.1, Choi and modified Choi (mChoi) criteria with normalised rather than absolute enhancement values in phase II of the STAR trial (comparing conventional continuation versus drug free intervals of tyrosine kinase inhibitor treatment in mRCC).

Methods: 44 patients underwent contrast-enhanced computed tomography (CE-CT) at baseline, 12 and 24 weeks post therapy. Automated software was used by 2 independent readers to evaluate 104 target lesions. Target lesion sum of longest diameter, normalised enhancement values (relative to aortic attenuation) and subsequent percentage change at 12 and 24-week CT were measured. Response categorisation into stable disease (SD), partial response (PR) or progressive disease (PD) was undertaken by RECIST 1.1, Choi and mChoi response criteria, and discrepant cases scored. Reader agreement was assessed by Cohen's kappa test.

Results: By RECIST 1.1, patients were 68%(n = 30)/41% (18)SD, 27%(12)/45%(20) PR, 2%(1)/9%(4) PD and 2%(1)/2%(1) CR at 12 and 24 weeks respectively. At 12 weeks 27 patients had discrepant categorisation: PR by both Choi/mChoi criteria but SD by RECIST in 17 and PR by CHOI, SD by mCHOI in 10. With absolute versus normalised enhancement values, 3 further patients would have remained as SD by mChoi at 12 weeks. At 24 weeks 14 remained discrepant: both Choi/mChoi PR but SD by RECIST in 10, PR by Choi but SD in mCHOI/RECIST in 4 patients. 11 previously discrepant patients by RECIST versus Choi/mChoi became concordant (8 PR, 3 PD) at 24 weeks. The concordance was excellent for RECIST (k 0.9, k 0.8) and mChoi (k 0.9 k 0.79), and good/excellent reader for Choi criteria (k 0.76 k1.0) at 12 and 24 weeks respectively.

Conclusions: Early response, confirmed at 24 weeks, was more frequent for Choi/mChoi than RECIST. Substantial/excellent agreement was noted in response categorisation with normalised versus absolute enhancement indicating this is a potentially robust approach.

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Legal entity responsible for the study: Leeds institute of clinical trials research

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Disclosure: F. Thistlethwaite: Previous ESMO travel and accommodation reimbursement by Ipsen and Bristol Meyers Squibb, consultant for Pfizer and Bristol-Meyers Squibb and received research funding from Pfizer, Novartis and Aveo. All other authors have declared no conflicts of interest.

891P Outcomes of patients with metastatic renal cell carcinoma (mRCC) who were treated with second-line (2L) vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGFR-TKI) after first-line (1L) immune checkpoint inhibitor (ICI) therapy

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Background: ICI therapy is an established strategy in mRCC after progressive disease on VEGFR-TKI. Little data exists in the reverse sequence on response rate, progression-free survival (PFS), safety, and tolerability of TKI after 1L ICI therapy.

Methods: This is a retrospective analysis of patients with mRCC treated from 2015 to present with 1L ICI, followed by 2L TKI. Response assessment was provided by a blinded radiologist using RECIST 1.1. Descriptive statistics, Fisher's test and Wilcoxon rank sum test were used.

Results: We report on 27 clear-cell mRCC patients with follow-up of at least 8 weeks on TKI post 1L ICI. Median age at diagnosis was 58 years. 78% of patients had lung, 37% bone, 37% lymph node, and 7% liver metastasis. As 1L therapy, 7 patients received nivolumab, 17 received nivolumab + ipilimumab, and 3 received nivolumab + bevacizumab. All 27 patients had resolution of Grade 3/4 toxicities from ICI and progressive disease at the time of TKI initiation. Median time from discontinuation of ICI to initiation of TKI was 4.1 weeks (range 0-23.3 weeks). 11 patients (41%) had PR (8 of whom had $\geq$40% tumor reduction), and 16 (59%) had SD as best response to TKI. Median PFS was 10.0 months (95% CI 6.8, not applicable). 9 patients discontinued 2L TKI after a median of 26.3 weeks (range 4.6-44 weeks), 8 patients because of PD and 1 because of toxicity. 2 patients developed Grade 3 transaminitis and 3 patients Grade 3 hand-foot skin reaction. Age, sex, IMDC risk score, nephrectomy status, and TKI agent did not predict PR or SD.

Table: 891P

Variable	Total n (%)	PR (n)	SD (n)	P value
Male	19 (70)	7	12	0.68
Female	8 (30)	4	4	
Localized at presentation	9 (33)	7	2	0.01
Metastatic at Presentation	18 (67)	4	14	
IMDC good risk	4 (15)	3	1	0.47
IMDC intermediate risk	19 (70)	7	12	
IMDC poor risk	4 (15)	1	3	
Nephrectomy	21 (78)	10	11	0.35
Primary in-situ	6 (22)	1	5	
Pazopanib	8 (30)	4	4	0.37
Axitinib	12 (44)	3	9	
Cabozantinib	7 (26)	4	3	

Conclusions: In this small retrospective study, we observed a high response rate (41%), median PFS 10 months, and manageable toxicity in patients with mRCC treated with TKI after ICI. No patients had outright PD on 2L TKI after ICI.

Legal entity responsible for the study: MD Anderson Cancer Center Dept of Genitourinary Medical Oncology

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892P Treatment beyond progression in patients with advanced RCC participating in the expanded access programme (EAP)

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Background: Response patterns of immunotherapies differ from those seen with other approved cancer therapies. Therefore, immunotherapy clinical trials generally allow patients (pts) to continue treatment beyond investigator-assessed radiographic progressive disease (PD) as long as there is ongoing clinical benefit, but to date no data have been reported regarding treatment beyond PD in routine clinical practice. Here, we report the analysis about the subgroup of pts treated beyond initial PD in the Italian cohort of nivolumab EAP.

Methods: Nivolumab was available upon physician request for pts aged ≥18 years who had relapsed after a minimum of one prior systemic treatment for stage IIIB/stage IV RCC. Nivolumab 3 mg/kg was administered intravenously every 2 weeks to a maximum of 24 months. Pts included in the analysis had received ≥ 1 dose of nivolumab and were monitored for adverse events (AE) using Common Terminology Criteria for Adverse Events. Patients could continue treatment beyond PD as long as they met the following criteria: investigator-assessed clinical benefit, absence of rapid PD, tolerance of drug, stable performance status and no delay of an imminent intervention to prevent serious complications.

Results: Of 389 nivolumab-treated pts, 231 pts (59%) had PD. Of those, 100 pts (43%) were treated beyond PD. Before being treated beyond PD, the disease control rates (DCR) was 23%, with 5 partial responses (PR) and 18 stable diseases (SD). Post PD, 28 of all pts treated beyond PD achieved a non-conventional benefit, meaning a subsequent tumor reduction or stabilization in tumor lesions. With a median follow-up of 9.2 months (0.1-17.0), 1 year overall survival was 73.5% in pts treated beyond PD and 43.5% for pts who progressed but were not treated beyond PD. The safety profile was consistent to what already observed in the general population.

Conclusions: As already observed in previous studies, these preliminary EAP data seem to confirm that a proportion of pts who continued treatment beyond PD demonstrated sustained reductions or stabilization of tumor burden, with an acceptable safety profile. Further investigation is warranted in order to better define pts who can benefit from treatment beyond PD.

Legal entity responsible for the study: Prof. Enrico Cortesi

Funding: Bristol-Myers Squibb

Disclosure: All authors have declared no conflicts of interest.

893P Improved long-term clinical outcomes and safety profile of sunitinib dosing schedule with 4/2 switched to 2/1 in patients with metastatic renal cell carcinoma

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Background: Adverse events (AEs) have been a key issue for sunitinib administration with a standard dosing schedule. We aimed to identify the survival benefit and safety of alternative dosage schedules for sunitinib in patients with metastatic renal cell carcinoma (mRCC).

Methods: Clinicopathologic and survival data of patients treated with sunitinib as first-line therapy were retrospectively reviewed. Patients were classified into three groups: a standard dosing schedule (4/2 schedule), alternative dosing schedule (2/1 schedule), and switched dosing schedule (4/2-2/1 schedule). Treatment-related AEs were recorded and evaluated. Progression-free survival (PFS), overall survival (OS), and potential risk factors were also analyzed.

Results: A total of 99 patients were included. Seventy-five (75.8%) patients were initially administrated with a 4/2 schedule of sunitinib, while 24 were started with the 2/1 schedule. During treatment, 45 (60.0%) patients with an initial 4/2 schedule switched to a 2/1 schedule (4/2-2/1 schedule) due to severe AEs or poor tolerance. The median follow-up time was 37 months. Compared to that with a 4/2 schedule, patients with a 2/1 schedule had a much lower incidence of grade 3/4 AEs (69.6% vs. 40.6%, $p = 0.001$). Overall, the 4/2-2/1 schedule was associated with the best survival benefits. Among the 4/2, 2/1, and 4/2-2/1 schedule groups, the median PFS was 12.5, 11.0, and 25.0 months, respectively ($p = 0.003$), and the median OS was 21.0, 28.0, and 52.0 months, respectively ($p = 0.030$). Multivariate analysis identified the 4/2-2/1 schedule as an independent factor predicting favorable PFS. Although without statistical significance, 4/2-2/1 schedule could decrease 55% risk of death. Furthermore, patients with unfavorable IMDC risk seemed to have more opportunity to achieve better survival from the 4/2-2/1 dosing schedule.

Conclusions: Among the three dosing schedules in the treatment of mRCC, patients with a 4/2-2/1 schedule could minimize treatment-related toxicities; more importantly, patients with 4/2-2/1 schedule could achieve a superior survival benefit. However, prospective clinical trials are required to identify the optimal sunitinib schedule.

Legal entity responsible for the study: Sichuan University

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Disclosure: All authors have declared no conflicts of interest.

894P A retrospective study of the management of metastatic renal cell carcinoma brain tumors

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Background: The purpose of this retrospective monocentric review was to evaluate the different techniques of stereotactic radiosurgery in the management of brain tumors from renal cell carcinoma (RCC).

Methods: From 2005 to 2015, 120 patients, with a total of 398 brain metastasis of RCC, were treated at least by stereotactic radiosurgery. Median age was 58 years (31–82). Median Karnofski performance status was 90 (50-100). One hundred ten tumors (92%) were clear cell carcinoma. Ninety-nine patients (82.5%) have undergone nephrectomy. The median time between the diagnosis of RCC and the first brain metastasis was 24 months (0-252).

Results: The median number of tumors per patient was 2 (1-46). The median diameter of the tumors was 13 mm (1-60). For the 120 patients, 222 procedures of treatment were recorded and 187 stereotactic irradiations were reviewed. Sixty-one patients (226

metastasis) were treated by Gamma Knife Surgery (GKS) and received a median dose on the 50% prescription isodose of 18 Gy (14-22). The minimal and maximal median dose was respectively 18.4 Gy (12.5-40.1) and 36 Gy (23.3-51.2). Sixty-three patients (136 metastasis) were treated by linear accelerator (photon 10 MV). The minimal (isodose 70%) and maximal (isocentre) median dose were respectively 16 Gy (9.8-25.8) and 20.3 Gy (15.3-33.74). The median disease-free survival time is 5.5 months (0-252). The median survival time between the first brain metastasis diagnosis and death is 13.5 months (0.5-147). The tumor growth control rates at 3, 6, 12 months are respectively 86%, 62%, 36%. Following the 187 stereotactic irradiations, 95 (51%) cerebral disease progressions are recorded, after a median time of 5 months (1-81); 81 progressions (85%) are due to new lesions and 25 (26%) due to local failures. Analyses of prognostic factors related to survival are still in progress.

Conclusions: Stereotactic radiosurgery is associated with a high local control of brain metastasis from RCC without whole brain radiotherapy. The two described modalities present different characteristics whose advantages will be further discussed with the assessment of prognostic and predictive factors of local control.

Legal entity responsible for the study: Assistance Publique des Hôpitaux de Paris (APHP)

Funding: None

Disclosure: All authors have declared no conflicts of interest.

895P SPAZO2 (SOGUG): Validation of the international metastatic database consortium (IMDC) prognostic classification for targeted therapies as 2nd-line after 1st-line pazopanib (1stPz) in metastatic renal cell carcinoma (mRC)

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Background: Only 2% of pt included in the IMDC prognostic model for 2nd-line targeted agents in mRC had received 1stPz (Ko, Lancet Oncol 2015). We aimed to validate the IMDC model for this population of patients receiving 1stPz.

Methods: SPAZO2 (NCT03091465) was a retrospective real-world study to analyze the effectiveness of 1stPz and subsequent therapies in mRC in several settings in every day practice. Data from 530 pt treated with frontline pazopanib outside CT in 50 centers in Spain were collected by investigators, but monitored and entered in a database by an external CRO.

Results: A total of 285 pt received antiVEGF or mTOR inhibitor as 2nd line (37.6% everolimus, 2.5% temsirolimus, 36% axitinib, 9.9% sunitinib, 8.3% sorafenib, 2.9% cabozantinib, 2.1% pazopanib, 0.4% beva-Inf, 0.4% savolitinib), 242 after true progression and 43 due to other causes after 1stPz. Unlike in IMDC, no pt had received 1st-line immunotherapy. Mean age was 66 y, 67.7% were male, 74.4% nephrectomized, and 12.3% pure nonclear-cell. Metastatic sites were: lung 74%, lymph nodes 55%, bone 36%, soft tissue/skin 27%, liver 24.8%, CNS 7%, adrenal gland 5%, pleura/peritoneum 6%, pancreas 5%, kidney 3% and other organs 2%. Classification of pt into the IMDC risk groups were: favorable (FR, 14.4%), intermediate (IR: 64.2%), or poor (PR: 21.4%). Median follow-up since 2nd-line was 29 mo; 67% of pt has progressed, 64% had received or subsequent lines, and 73% had died. Response, PFS and OS (and 95%CI) since 2nd-line are showed in the table. Differences in PFS and OS were statistically significant among groups (FR vs IR and FR vs PR). The C-Index was 0.635 (95%CI: 0.627 – 0.642). We also provide an estimation of outcomes according to if pt received 2ndline after "true progression" or due to any cause.

Conclusions: Our results validate the use of the IMDC prognostic classification as a discrimination tool, for predicting prognosis in pt receiving 2nd-line targeted therapies after pazopanib in mRC. Pt who received 2nd-line after true progression had a poorer prognostic than the predicted by the IMDC.

Clinical trial identification: NCT03091465

Legal entity responsible for the study: SOGUG

Funding: Novartis

Disclosure: B. Pérez-Valderrama: Consulting/Advisory role for Astellas Pharma, Novartis, Pfizer, Pierre Fabre, Bayer, Sanofi, Bristol-Myers Squib and Roche. J. Arranz Arija: AdBo from Novartis and Pfizer. G. de Velasco: Consulting and Advisory board for Pfizer, Novartis, Bayer, Roche. M.A. Gonzalez Del Alba Baamonde: Advisory boards for Novartis, Pfizer, Bristol-Myers Squib, Ipsen. All other authors have declared no conflicts of interest.

896P A Phase (Ph) 1 dose finding study of X4P-001 (an oral CXCR4 inhibitor) and axitinib in patients with advanced renal cell carcinoma (RCC)

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Background: X4P-001 is an oral, selective, allosteric inhibitor of the chemokine receptor CXCR4, and has been shown to down-regulate hypoxia inducible factor-2α (HIF-2α) and myeloid-derived suppressor cell (MDSC) trafficking in the tumor microenvironment. In multiple RCC xenograft models, the addition of X4P-001 to tyrosine kinase inhibitors (TKIs), including axitinib, increases the efficacy and delays the onset of TKI resistance.

Methods: This is an ongoing phase 1/2 open-label study of X4P-001 in combination with axitinib in patients (pts) with histologically confirmed clear cell RCC who have received 31 prior systemic therapy. The Ph1 portion of the study evaluates safety, tolerability, PK, PD and anti-tumor activity of the combination using a 3 + 3 dose escalation schema (escalating doses of X4P-001+ axitinib at 5 mg BID).

Results: As of 27 April, 2017, sixteen (16) pts were enrolled in the Ph1 portion of the study. The median age was 64 years (range 50-76) and pts had received a median of 2 prior lines of therapy (range 1-5). The doses tested were 200 mg BID, 400 and 600 mg QD of X4P-001 + axitinib. Two doses limiting toxicities (DLTs) were observed at the X4P-001 600 mg QD dose level: one pt had multiple grade (G) 2 adverse events (AEs), including anorexia, cognitive disturbance, fatigue, nausea, vomiting, and somnolence; another pt had G3 dyspnea and fatigue. The MTD/RP2D was determined to be 400 mg QD of X4P-001 + axitinib. Treatment-related AEs (≥ 10%) of any grade were fatigue, diarrhea, hypertension, nausea, headache, anorexia, vomiting, dysphonia, proteinuria, dry eye, dry mouth, arthralgia, chest pain, cognitive disorder, dysgeusia, stomatitis, weight loss, and elevated creatinine. Treatment-related G3/4 AEs (≥ 10%) were fatigue and hypertension. In addition, one pt had SAE due to G2 diarrhea and G2 creatinine elevation. Of the 9 clinically evaluable pts, 3 had confirmed partial response, 5 had

Table: 895P

	SPAZO2				IMDC			
	Overall	FR	IR	PR	Overall	FR	IR	PR
ORR	14.6%	22.5%	15.8%	5.5%	Not reposted			
Median PFS (1)*	5.1 (4-6)	11.5 (5-18)	5 (4-6)	3 (2-4)	3.9	Not reported		
Median PFS (2)*	4.7 (4-5)	9.7 (4-15)	4.8 (4-6)	3 (2-4)				
Median OS (1)*	11.3 (9-13)	24.4 (18-30)	12.7 (10-15)	6.5 (5-8)	12.5 (11-14)	35.3 (28-48)	16.6 (15-18)	5.4 (5-7)
Median OS (2)*	11.1 (9-13)	19.8 (12-27						

*Months; 1: 2nd-line due to any cause (N = 285); 2: 2nd-line due to progression to Pz (N = 242).

stable disease, and 1 had progressive disease. Median duration on treatment was 6.0 months (range 4.6-12.1).

Conclusions: The combination treatment of X4P-001 and axitinib is well tolerated with preliminary evidence of clinical activity. The Ph2 portion of the study is ongoing.

Clinical trial identification: NCT02667886 First received: January 20, 2016

Legal entity responsible for the study: X4 Pharmaceuticals

Funding: X4 Pharmaceuticals

Disclosure: D.F. McDermott: Paid consultant to Bristol-Myers Squib, Pfizer, Merck, Novartis, Eisai, Exelixis, Array BioPharm, Genentech BioOncology and receives research support from Prometheus S. Blanchette, L. Gan: Employee of X4 Pharmaceuticals. M.B. Atkins: Compensated consultant for Bristol-Myers Squibb, Merck, Roche, Pfizer, Novartis, Peleton, AstraZeneca, Nektar, Acceleron, Eisai and Exelixis and serve on Advisory Boards for X4 Pharma, Merck, Novartis, Roche, Pfizer, Galactone, Agenus and AVEO. All other authors have declared no conflicts of interest.

897P Efficacy and safety data in elderly patients (pts) with metastatic renal cell carcinoma (mRCC) included in the nivolumab expanded access program (EAP) in Italy

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Background: The risk of developing renal cell carcinoma (RCC) increases with age, and given the constant gain in life expectancy of the general population, RCC is frequently observed in the elderly. More than 80% of cancer pts aged ≥ 70 years have at least one comorbidity requiring treatment, leaving them exposed to drug interactions. Due to high frequency of comorbidities, these pts are often under-represented in clinical trials. The purpose of this analysis is to evaluate the feasibility of treatment with nivolumab in the elderly (≥ 70 years) and very elderly (≥ 75 years) in the EAP in Italy, given a more realistic picture of real world setting.

Methods: Nivolumab was available upon physician request for pts aged ≥18 years who had relapsed after at least one prior systemic treatment in the advanced or metastatic setting. Nivolumab 3 mg/kg was administered intravenously every 2 weeks to a maximum of 24 months. Pts included in the analysis had received ≥ 1 dose of nivolumab and were monitored for adverse events (AEs) using Common Terminology Criteria for Adverse Events.

Results: Of 389 Italian pts with mRCC enrolled in the EAP in Italy 125 pts (32%) had ≥70 years and 70 (18%) had ≥75 years. With a median follow-up of 9.8 months (0.1-16.2) in the elderly population (≥70 years), the disease control rate (DCR) was 58% including 1 patient in complete response (CR), 32 pts in partial response (PR) and 40 patients in stable disease (SD). Regarding the very elderly population (≥75 years), with a median follow-up of 9.8 months (0.1 -14.9), the DCR was 60% including 1 patient with CR, 19 pts with PR and 22 with SD. As of May 2017, 6 and 12 months overall survival (OS) rate were 87.2% and 77.8% respectively in the elderly population. Regarding the very elderly, the 6 and 12 months OS rate was 83.6% and 77.7%, respectively. The safety profile was consistent to what already observed in the general population.

Conclusions: These results suggest that elderly population can benefit from nivolumab treatment with safety results consistent to what previously reported, supporting the use of nivolumab in this subpopulation.

Clinical trial identification: CA209-99M

Legal entity responsible for the study: Sergio Bracarda coordinator Italian RCC EAP Group

Funding: None

Disclosure: All authors have declared no conflicts of interest.

898P Immune expression profile and sunitinib benefit in metastatic clear cell renal cell carcinoma (ccRCC)

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Background: The identification of predictive biomarkers may be useful to select anti-angiogenic or immunotherapy treatment in renal cell carcinoma. We here investigated the immune expression profile in sunitinib (SU) or anti-PD1/PD-L1 treated ccRCC patients.

Methods: Forty-two metastatic ccRCC patients treated with SU and 10 patients treated with anti-PD1/PD-L1 antibodies were included in this retrospective biomarker study. 730 immune-related genes (nCounter® PanCancer Immune Profiling Panel, Nanostring) were tested in FFPE tumor specimens. Different immune gene signatures were correlated with clinical outcome. A differential expression analysis between refractory (progression-free survival (PFS) < 3 months) and sensitive (PFS > 3 months) patients to SU and anti-PD1/PD-L1 therapies was performed.

Results: Patients who achieved a partial or complete (P/CR) response with SU had a higher score of B cell, CD8 T cell, T cell, Th1 cell, Th2 cell, Treg cell and Stromal signatures. Moreover, these signatures were predictive of P/CR to sunitinib (p-value for odds ratio < 0.05). T cell signatures (CD8 T cell, T cell, Th1 cell, Th2 cell and Treg cell) were correlated with a better PFS, while activated dendritic cell (aDC) and stromal signatures were correlated with a better OS (Table). In the cohort of anti-PD-1/PD-L1 treated patients, no differences in the immune signatures were found between responders and no-responders to these drugs. However, differential expression analysis revealed a single gene, TIM-3, that was associated with resistance to anti-PD1/PD-L1 therapies and benefit to SU in ccRCC patients.

Table: 898P

Signatures	Progression-Free Survival		Overall Survival	
	HR (95% CI)	P	HR (95% CI)	P
CD8Tcell	0.57 (0.37 – 0.89)	0.01235	0.64 (0.39 – 1.03)	0.0684
Th1cell	0.62 (0.41 – 0.95)	0.02841	0.70 (0.43 – 1.14)	0.1491
Tcell	0.68 (0.48 – 0.98)	0.03951	0.79 (0.52 – 1.19)	0.2649
Tregcell	0.67 (0.45 – 0.98)	0.04126	0.76 (0.49 – 1.18)	0.2146
Th2cell	0.48 (0.24 – 0.97)	0.04155	0.62 (0.30 – 1.26)	0.1853
Stromal	0.72 (0.50 – 1.03)	0.06923	0.64 (0.43 – 0.96)	0.0291
Bcell	0.69 (0.47 – 1.03)	0.07271	0.74 (0.48 – 1.14)	0.1698
aDC	0.78 (0.46 – 1.34)	0.37136	0.53 (0.29 – 0.95)	0.0330
iDC	0.91 (0.52 – 1.58)	0.74005	0.69 (0.37 – 1.32)	0.2649

Conclusions: T cell signatures may be associated with benefit to SU in ccRCC. The value of TIM-3 as a potential biomarker in ccRCC merits further exploration.

Legal entity responsible for the study: Hospital Clínic de Barcelona

Funding: Fundació Clínic per a la Recerca Biomèdica

Disclosure: All authors have declared no conflicts of interest.

899P Interim results from PAZOREAL: A non-interventional study to assess effectiveness and safety of pazopanib and everolimus in the changing mRCC treatment landscape

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Background: The treatment (tx) of metastatic renal cell carcinoma (mRCC) has markedly changed over the last decade with the introduction of targeted therapies including vascular endothelial growth factor receptor (VEGFR) and mammalian target of rapamycin (mTOR) inhibitors. Current tx recommendations include the VEGFR inhibitor pazopanib (PAZ) as first-line option and the mTOR inhibitor everolimus (EVE) after VEGF-targeted therapy. The approval of programmed cell death 1 (PD-1) checkpoint inhibitor nivolumab (NIVO) in 2016 provides an additional second-line option.

Methods: PAZOREAL is a prospective, non-interventional study to evaluate the effectiveness, tolerability, safety and quality of life on the routine tx of 450 adult patients (pts) with histologically confirmed mRCC treated with first-line PAZ, second-line EVE or NIVO, or third-line EVE after NIVO. The main objective is time on drug (TD) in the respective tx lines and overall, other objectives include overall survival, dosing parameters, safety and quality of life.

Results: Between December 2015 and March 2017, 305 pts have been enrolled; 302 in the first-line PAZ cohort and 3 in third-line EVE after NIVO. The latter cohort was opened for documentation after approval of NIVO. 266 first-line pts had a documented first intake of PAZ and were eligible for analysis; 201 (75.6%) had a clear-cell histology. Median TD on PAZ was 6.5 months. For 98 pts (36.8%) discontinuation of PAZ tx was reported. The main reasons were progressive disease (N = 36), followed by toxicity (N = 18) and (serious) adverse event (N = 13). Details on subsequent tx with NIVO or EVE were documented for 24 and 4 pts, respectively, while 8 pts started other therapies in second line. During PAZ tx, the most frequently reported treatment-emergent adverse events (TEAE) of grade 1/2 were diarrhea (N = 57), nausea (N = 36), and fatigue (N = 24), of grade 3/4 were hypertension (N = 11), diarrhea and anemia (each N = 4). Fatal TEAEs were reported in 28 pts with progression being the most common term.

Conclusions: PAZ is an effective and safe first-line therapy for pts with mRCC in a real life setting. Second line therapy has rapidly shifted towards NIVO.

Clinical trial identification: BfArM AWB No. 6687

Legal entity responsible for the study: Novartis Pharma GmbH

Funding: Novartis Pharma GmbH

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900P Phase II study of individualized sunitinib (SUN) as first-line therapy for metastatic renal cell cancer: Pharmacokinetic data

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Background: Higher SUN exposure is associated with better outcomes but SUN PK on day 28 does not correlate with toxicity (# 363, ASCO-GU 2012).

Methods: Toxicity-driven dose/schedule individualization was tested in a prospective phase II study where all pts start on 50 mg/day (d). Pts with minimum toxicity on d 28 are dose escalated to 62.5 mg and then 75 mg. Samples for SU011248 and SU012662 were drawn on day 14 on the first course (100 pts) and again after the optimal dose/schedule had been established (58 pts). 11 patients had 2-3 more samples drawn during continued Rx on the optimal dose.

Results: 117 pts were enrolled. Of 108 pts evaluable for response, dose was escalated in 20 pts to 62.5 mg (12 pts) and then to 75 mg (8 pts). In 49 pts eligible for dose reduction by standard criteria, a 50 mg dose was maintained but for 7 - 24 d. Dose was reduced to 37.5 mg in 22 pts and to 25 mg in 10 pts with individualized days on Rx. For 100 pts sampled on the first course the mean concentration (standard error) was 93.8 (3.0) and 29.8 (1.4) ng/mL for SU011248 and SU012662 respectively. For 58 pts, sampled again when optimal dose was established, the mean change from the 1st course for SU011248 and SU012662 was significantly different between dose levels ($P < 0.001$, Table). The same was true even after dose optimization ($p = 0.01$). The mean PK values declined over time in 27 pts that remained on 50 mg and a continued decline was seen in 6/11pts with continued sampling. There was no significant difference in PFS and OS between dose levels for all 117 pts.

Table: 900P

Dose level (n pts)	SU011248 (standard error) During 1st course ng/mL mean change at optimal dose	SU012662 (standard error) During 1st course ng/mL mean change at optimal dose
50 mg (n = 27)	90.7 (5.2) −11.8 (5.6)	27.6 (2.6) 0 (2.3)
< 50 mg (n = 13)	95.4 (10.1) −22.6 (12.7)	33.6 (4.6) −12.7 (4.4)
>50 mg (n = 18)	77.1 (5.7) +29.6 (10.6)	24.1 (2.6) +12.4 (2.5)
After optimization	**SU011248 (SE) at optimal dose**	**SU012662 (SE) at optimal dose**
50 mg (n = 27)	78.9 (4.7)	27.5 (2.3)
< 50 mg (n = 13)	72.8 (8.0)	21.7 (2.8)
>50 mg (n = 18)	106.7 (11.9)	36.5 (3.6)

Conclusions: While dose individualization corrects for some of the differences in PK values on the 1st Rx course, differences remain even after dose optimization emphasizing the importance of pharmacodynamics for toxicity and outcome. An ongoing dose optimization may be important to correct for the decline in PK over time.

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Legal entity responsible for the study: Dr. Georg A Bjarnason and the Sunnybrook Research Institute

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901P Safety and efficacy of Cabozantinib for metastatic renal cell carcinoma (mRCC): real world data from an Italian Expanded Access Program (EAP)

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Background: Final results from the randomised phase III METEOR trial confirmed a survival benefit of cabozantinib over everolimus in patients (pts) with advanced clear-

cell renal cell carcinoma who progressed after at least one previous antiangiogenic inhibitor. The EAP provided the opportunity to treat pts in real world clinical practice.

Methods: Data were collected from 91 pts treated with cabozantinib across 23 Italian hospitals. Cabozantinib was available, upon physician request, from September to December 2016. Pts were aged 18 years and older, with mRCC and measurable disease, with Perfomance Status (ECOG) 0 to 2, who had relapsed after one or more prior systemic treatment. 73 pts had clear-cell RCC, while the other 18 had non-clear-cell histologies (type II papillary and chromophobe). The most frequent sites of disease were: lung 53 (58%), lymph nodes 41 (45%), bone 28 (31%), liver 15 (16%) and brain 5 (5%); 42 (46%) pts had two or more sites of disease. Cabozantinib was administered orally at 60 mg once a day in 28 days-cycles. Dose reductions to 40 or 20 mg were allowed if toxicity was encountered. Pts were monitored for adverse events (AEs) using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v.4.0. The aim of this analysis was to evaluate the safety and activity of cabozantinib in a large unselected population.

Results: Cabozantinib was administered as second line therapy in 28 (30%) pts, as III line in 18 (19%) pts and as further lines in the remaining 45 (51%) pts. At the time of our analysis, grade 3 and 4 AEs were observed in 21% of pts. Among 91 pts, only 5 (5%) discontinued treatment due to AEs. The best overall response was partial in 28 cases (31%), whereas 23 (25%) pts had stable disease and 23 (25%) had progressive disease; 17 pts (18%) have not reached the first response assessment. With a median follow-up of 4 months, the median progression-free survival observed was 3.5 months irrespective of the line of treatment.

Conclusions: Our data suggest that cabozantinib is safe and active in a large unselected population treated according to everyday clinical practice.

Legal entity responsible for the study: Fondazione IRCCS Istituto Nazionale dei Tumori of Milan

Funding: None

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902P Prognostic factors for overall survival of patients with advanced renal cell carcinoma – data from the German prospective RCC-Registry

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Background: The identification of prognostic factors is a central question in oncology. They help to predict the course of disease and ideally support the oncologist in treatment decision making in clinical practice. We analysed prognostic factors identified by MSKCC and additional factors for the overall survival (OS) of patients (pts) treated with currently approved agents.

Methods: The prospective German renal cell carcinoma (RCC) Registry includes pts with advanced or metastatic renal cell carcinoma at start of systemic first-line therapy. > 300 oncologists are recruiting pts since 2007. Pts and tumour characteristics, data on all systemic therapies and outcome are collected. The prognostic factors for OS were assessed using a multivariate cox regression model.

Results: Median OS of the 1039 pts (median age 70 years) was 18.6 months (95% CI 16.0 - 20.5 months, 55% events). Median OS in months for low, intermediate and high risk pts according to MSKCC 1999 was 27.3 (23.7-33.8, 48% events), 16.0 (12.7-18.8, 58% events) and 5.3 (3.7-7.2, 74% events). The following factors were significantly associated with shorter OS ($p < 0.05$: *; $p < 0.01$: **; $p < 0{,}001$: ***): higher age*, non-clear cell histology**, grading G3/4 at diagnosis*, Karnofsky Performance Status <80%***, haemoglobin < lower limit of normal (LLN)***, LDH >1.5x upper limit of normal (ULN)***. Factors significantly associated with longer OS were time from primary diagnosis to metastasis***, BMI 25-30 versus (vs) <25***, BMI>30 vs < 25***, lung metastasis only at start of treatment*, non-visceral metastasis only at start of treatment* and hypertension*. Factors not significantly associated with OS were sex, tumour stage at diagnosis (IV vs <IV), total calcium >ULN, tumour localisation (right/left), congestive heart failure, renal disease, diabetes and total nephrectomy.

Conclusions: 3 out of 5 MSKCC factors were significantly associated with OS in our cohort. Still, a clear separation of OS between pts with low, intermediate and high risk according to MSKCC could be confirmed. In addition, we identified novel factors also associated with OS.

Clinical trial identification: ClinicalTrial.gov registry: study number: NCT00610012

Legal entity responsible for the study: iOMEDICO AG

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Disclosure: P.J. Goebell: Received honoraria for paticipation in expert rounds and honoraria/support as a speaker from Astellas, AstraZeneca, Bayer, Bristol-Myers Squib, Eisai, Ipsen, Janssen, Novartis, Pfizer, Sanofi. M. Staehler: Consultant, Honoria and Research Funding: Pfizer, GlaxoSmithKline, Novartis, Bayer, AVEO, Ipsen, Exelixis, EISAI Consultant and Honoria: EUSAPharm, Astellas, Pelloton Consultant and Research funding: Roche Research funding: Immatics, Wilex. N. Marschner: Employed by iOMEDICO which performs the tumorregistry RCC as an CRO Member of advisory boards regarding RCC treatment and Travel grants: Roche, Novartis, Pfizer, Bayer, GSK Corporate sponsored research: Novartis, Pfizer Roche. All other authors have declared no conflicts of interest.

903P The efficacy and safety of sorafenib in patients with renal insufficiency of advanced renal cell carcinoma: Real- world data of sorafenib in Japan

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Background: Multiple treatment options are available for patients with advanced renal cell carcinoma (aRCC). However, the safety/efficacy data of these agents in patients with renal insufficiency are limited. To assess the safety/efficacy of sorafenib in aRCC patients with renal insufficiency, we analyzed the real-world data of a nationwide prospective post-marketing surveillance applying propensity score-matched cohorts.

Methods: A total of 3,255 patients with aRCC were enrolled, and 1,226 patients of whom were selected by propensity score matching for estimated glomerular filtration rate (eGFR) <45 (n = 613) and ≥45 (n = 613). Progression free survival (PFS), tumor response, adverse events (AEs), and doses of sorafenib were compared between the two groups.

Results: The median PFS in eGFR<45 and ≥45 was 7.4 months (6.4, 8.8) vs. 8.3 months (6.6, 9.0), respectively. Complete response rates were 1.8% and 3.0%, partial response rates were 24.3% and 26.4%, stable disease rates were 59.8% and 57.7% in eGFR <45 and ≥45, respectively. The mean starting dose was lower in eGFR <45 group (687 mg vs. 726 mg, $p < 0.0001$), but the median duration of treatment (6.1 vs. 6.6 months) and median daily dose (484 vs. 481 mg) were similar in both groups. The discontinuation rates due to AEs were similar in both groups. Any grade AEs observed ≥20% were hand-foot skin reaction (HFSR) (57.8%), hypertension (37.9%), rash (27.0%), and increases in lipase/amylase (26.9%), and diarrhea (23.1%). The common serious AEs were rash (7.6%), hepatic dysfunction (7.3%), bleeding (6.9%), HFSR (4.9%) and cytopenia (4.6%). The incidence of these common AEs was similar between the groups, except for cytopenia and renal failure which were higher in eGFR <45 group. In the both groups, the eGFR value did not change from the baseline over a year, and it also did not deteriorate even at the time of discontinuation.

Conclusions: Sorafenib has little impact on the renal function in almost all patients with renal insufficiency and provide the fine therapeutic effects for these aRCC patients.

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904P Inflammatory indexes strongly predict clinical outcome in patients (pts) with metastatic renal cell cancer (mRCC) treated with nivolumab: results from the Italian expanded access program (EAP)

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Background: Biomarkers for outcome after immune-checkpoint blockade in mRCC are needed. We aimed to verify the prognostic impact of inflammatory indexes based

on baseline values of neutrophils (N), lymphocytes (L) and/or platelets (P) in pts with mRCC included in the Italian nivolumab EAP.

Methods: Pts who had received ≥ 1 dose of nivolumab 3 mg/kg every 2 weeks in the Italian EAP after at least one prior systemic therapy for mRCC were enrolled in this study. The pre-treatment systemic immune-inflammation index (SII) defined as P×N/L, neutrophil-to-lymphocyte ratio (NLR) defined as N/L and platelet-to-lymphocyte ratio (PLR) defined as P/L were evaluated to identify a potential correlation with overall survival (OS). X-tile 3.6.1 software was used to identify cut-off values. OS was estimated by the Kaplan-Meier method and compared with the log-rank test. The impact of SII, NLR, and PLR on OS was evaluated by Cox regression analyses and on best overall response rate (ORR) by binary logistic regression.

Results: A total of 346 mRCC pts treated with nivolumab were included. SII ≥ 1375, NLR ≥ 3 and PLR ≥ 232 were considered as elevated levels (high risk groups). One-year OS in low and high SII group was 77% and 36%, respectively ($p < 0.0001$); 1-year OS in low and high NLR was 76% and 58%, respectively ($p < 0.0001$); 1-year OS in low and high PLR was 76% and 45%, respectively ($p < 0.0001$). Likewise, best ORR was higher in pts with low SII ($p = 0.008$), low NLR ($p = 0.06$) and low PLR ($p = 0.004$). In multivariate analysis adjusted for age, gender, risk score (MSKCC), ECOG performance status, presence of liver, brain and/or bone mets, SII, NLR and PLR, the model identified SII as the strongest factor associated with OS ($p < 0.0001$).

Conclusions: SII, NLR, and PLR are robust inflammatory prognostic factors for predicting outcome in mRCC pts treated with nivolumab. SII is a more powerful predictive system than the other inflammatory indexes for these pts.

Clinical trial identification: expanded access program

Legal entity responsible for the study: Italian RCC EAP Group

Funding: None

Disclosure: U. De Giorgi: advisory board Bristol-Myers Squib. All other authors have declared no conflicts of interest.

905P CORE-URO-01 study: comparison of safety and efficacy of pazopanib in first-line metastatic renal cell carcinoma (mRCC) with or without renal failure

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Background: Pazopanib has been approved for first-line treatment of patients (pts) with mRCC based on the prospective randomized trial that enrolled only pts with adequate renal function. There are no data on the efficacy and toxicity of pazopanib in pts with renal insufficiency (RI). The aim of this study is to investigate the effect of kidney function on treatment outcomes in pts treated with pazopanib for mRCC.

Methods: We retrospectively analyzed the data of the mRCC pts treated with pazopanib with respect to renal function in fourteen Italian institutions from January 2010 to June 2016. Baseline glomerular filtration rate (GFR) was calculated using the Modification of Diet in Renal Disease (MDRD) formula at the time of therapy initiation. Pts with MDRD<60 mL/min/1.73 m2 (group A) were compared with pts with MDRD≥60 mL/min/1.73 m2 (group B) in terms of response rates, progression free survival (PFS), overall survival (OS) and toxicities.

Results: Two hundred and twenty-nine pts with mRCC were included in this study: 128 pts in group A and 101 pts in group B. 68% of pts were male, median age was 67 years (34-88) and median CrCl was 49,7 ml/min in group A. In group B, 64% of pts were male, median age was 64 years (38-85) and median CrCl was 74 ml/min. Pts with MDRD<60 were more likely to have had a previous nephrectomy (87% vs 79%). Median PFS was 14 months (95% confidence interval [CI] 9.4-18.5) and 17 months (95% CI 11.4-22.8), OS was 30.5 months (95% CI 8-53) and 41.4 months (95% CI 21-62) for MDRD<60 group and MDRD≥60 respectively, with no statistical difference ($p = 0.6$). The disease control rate was 84% in group A, and 73% in group B ($p = 0.1$). About toxicity profile, no difference between the 2 groups was reported in terms of incidence of grade 1-2 (73% in group A vs 74% in group B, $p = 0.5$) and grade 3-4 (24% vs 33% respectively, $p = 0.2$). Dose reductions are statistically more frequent in pts in group A (66% vs 36%, $p = 0.04$), despite the same percentage of pts in both groups started at dose of 800 mg/day.

Conclusions: Although in this study it is necessary to reduce the dose of pazopanib more frequent in pts with RI, kidney function at therapy initiation does not adversely affect the efficacy and safety of pazopanib.

Legal entity responsible for the study: Cristina Masini

Funding: None

Disclosure: All authors have declared no conflicts of interest.

906P Impact of haptoglobin polymorphism on survival of renal cell carcinoma patients

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Background: Renal cell carcinoma (RCC) accounts for 2.4% of all malignancies worldwide with 338,000 estimated new cases globally in 2012. With 144,000 deaths annually, RCC is the 16th cancer-related death worldwide. In the last decade, the use of targeted therapy for patients with metastatic RCC has increased exponentially, especially since the breakthroughs with cabozantinib and nivolumab. Apart from the Heng criteria in 1st-line therapy, no robust biochemical markers exist for the prognosis of RCC patients. Here we assessed the prognostic value of haptoglobin (Hp) polymorphisms on survival of RCC patients.

Methods: At interim analysis, 53 metastatic RCC patients were enrolled and Hp phenotypes were determined prospectively. Survival data was retrieved from the electronic patient files. Kaplan-Meier survival analyses were performed for disease-free survival (DFS), progression-free survival (PFS) after 1st- and 2nd-line therapy, and overall survival (OS).

Results: Fifty-eight percent of patients were male. Hp distribution was 19%, 49% and 32% for Hp 1-1, 2-1 and 2- phenotypes, respectively. Median follow-up since development of metastatic disease was 4.7 years (95% CI 3.3 – 6.5). Lowest DFS was found in patients with Hp 2-2 phenotypes. This was significant when Hp 2-2 phenotypes were compared with Hp 1-1/2-1 phenotypes (hazard ratio [HR] = 1.93 [95%CI 1.12 – 5.75], $P = 0.0255$). No significant difference between Hp phenotypes was noticed for PFS after 1st-line therapy. After 2nd-line therapy, longest PFS was observed in patients with Hp 2-1 and 2-2 phenotypes which was better compared with Hp 1-1 phenotypes. Lastly, OS was found to be longer in patients with Hp 2-1 and 2-2 phenotypes, although no significance was observed versus patients with Hp 1-1 phenotypes. Median durations of survival and HRs versus Hp 1-1 phenotypes are given in Table.

Table: 906P Hp survival analysis

Cohort	Hp	N	Median survival	HR vs Hp 1-1	P-value
DFS (years)	1-1	9	0.6 (0.2 – 4.3)	1	0.0616
	2-1	19	2.3 (0.6 – 5.0)	0.73 (0.34 – 1.59)	
	2-2	14	0.5 (0.1 – 0.9)	1.54 (0.60 – 3.97)	
PFS 1st-line (months)	1-1	9	11.7 (2.4 – 17.6)	1	0.7529
	2-1	26	14.7 (6.5 – 28.7)	0.90 (0.33 – 2.45)	
	2-2	17	6.7 (4.2 – 52.2)	1.20 (0.40 – 3.54)	
PFS 2nd-line (months)	1-1	5	3.2 (0.9 – 3.9)	1	0.0001
	2-1	16	6.2 (5.4 – 17.6)	0.21 (0.03 – 0.87)	
	2-2	12	16.4 (6.9 – 27.6)	0.13 (0.02 – 0.67)	
OS (years)	1-1	10	1.7 (1.2 – 2.7)	1	0.4205
	2-1	26	3.8 (2.3 – 6.2)	0.56 (0.20 – 1.60)	
	2-2	17	3.5 (1.6 – 7.1)	0.61 (0.20 – 1.87)	

Conclusions: Interim analysis shows that Hp phenotype has prognostic potential, especially in DFS and PFS during 2nd-line therapy. Continuation of the research on this topic is warranted.

Legal entity responsible for the study: Ghent University

Funding: Ghent University

Disclosure: All authors have declared no conflicts of interest.

907P Impact of CYP3A4*22 on pazopanib pharmacokinetics in cancer patients

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Background: Pazopanib is characterized by a large interpatient variability in systemic drug exposure. As pazopanib trough levels (>20.5 mg/L) are correlated with clinical outcome (Suttle et al, BJC 2014) in metastatic renal cell carcinoma (mRCC) patients, it is vital to identify factors that influence pazopanib pharmacokinetics (PK). The objective of the current analysis was to evaluate if single nucleotide polymorphisms (SNPs) in the metabolic pathway of pazopanib (i.e. *CYP3A4*, *ABCB1* and *ABCG2*) affect systemic pazopanib concentrations.

Methods: We analyzed 97 patients who participated in 3 pazopanib PK studies. Starting point of the current analysis was a population PK model for pazopanib (Yu et al, Clin Pharmacokinet 2017). Four SNPs located on 3 genes, that were associated with decrease of function were analyzed using real time PCR: *CYP3A4 15389 C>T (*22)*, *ABCB1 3435 C>T*, and the *ABCG2* SNPs *421 C>A*, and *34G>A*. The influence of these SNPs on pazopanib bioavailability and clearance (CL) was explored with NONMEM. Statistical significance was determined with the likelihood ratio test using the objective function value (OFV). Trough concentrations (C_{trough}) at 6 weeks after start with doses of 400 to 800 mg once daily (OD), were simulated. A threshold C_{trough} of 20.5 mg/L was used as reference.

Results: From 3 patients, insufficient DNA was isolated to run a PCR analysis. All SNPs were in Hardy-Weinberg equilibrium. Eleven patients (12%) had a variant allele at *CYP3A4*22*, all of whom were heterozygous. Incorporation of *CYP3A4*22* in the NONMEM model resulted in a 35% lower CL for the variant carriers (0.18 L/h vs 0.27 L/h; $\Delta OFV = -7.8$; $P < 0.01$). Simulated median C_{trough} of patients with *CYP3A4*22* with 400 mg OD, 600 mg OD or 800 mg OD were 16 mg/L, 25 mg/L and 33 mg/L, respectively. Simulated C_{trough} for the population excluding the *CYP3A4*22* heterozygotes after 800 mg OD was 21 mg/L. No effect of the *ABCB1* or *ABCG2* SNPs on systemic concentrations were found.

Conclusions: Our analysis shows that *CYP3A4*22* carriers have a clinically relevant lower pazopanib CL. Prospective analysis should point out whether *CYP3A4*22* carriers are at risk for more toxicity and require a lower pazopanib starting dose.

Legal entity responsible for the study: Erasmus MC, Rotterdam, The Netherlands

Funding: None

Disclosure: All authors have declared no conflicts of interest.

908P Association between biopsychosocial distress (BPSD) and overall survival (OS) in patients with metastatic renal cell carcinoma (mRCC)

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Background: Depressive symptoms have been associated with poorer OS in pts with mRCC (Prinsloo et al J Behav Med 2015). In other malignancies, BPSD has also been linked to poorer OS, but in mRCC, this association is unclear.

Methods: From a single institution, clinicopathologic information from pts with mRCC diagnosed between 2001 and 2016 were collected. Corresponding data from an electronic survey tool was obtained, comprised of 22 core items spanning physical, practical, functional and emotional domains. Each item was self-assessed by the pt on a 5-point Likert scale. The cumulative score was used to characterize BPSD as either as low BPSD (not a problem/mild) vs high BPSD (moderate/severe/very severe). Associations between BPSD level and clinicopathologic criteria (e.g., Heng risk) were interrogated, and OS was compared between patients characterized as low BPSD vs high BPSD.

Results: A total of 102 pts (28.4% F/71.6% M) were assessed with a median age of 63 (range, 24-80). 73.4 and 26.6% pts were characterized as having good/intermediate and poor risk by Heng criteria, respectively. 79.3% pts and 20.7% pts were characterized as having low and high BPSD, respectively. No association was found between BPSD and age or gender. However, married patients have a longer survival (48.65 mos vs 34.52 mos, P=.07). Pts with poor risk mRCC were noted to have a higher BPSD as compared to pts with mild BPSD (75% vs 25%, P=.22). Median OS in the overall cohort was 44.2 months (mos). Although not statistically significant, a trend towards prolonged OS in pts with low BPSD vs high BPSD was observed (45.81 mos vs 35.95 mos, P = 81).

Conclusions: Our study suggests a potential link between Heng risk and BPSD, and further shows a compelling trend towards poorer OS in pts with higher BPSD. These results warrant confirmation in larger series. Targeted interventions to address elements related to BPSD have the potential to improve patient outcomes and should be developed.

Legal entity responsible for the study: City of Hope Comprehensive Cancer Center

Funding: None

Disclosure: All authors have declared no conflicts of interest.

909P Treatment reality and outcome data of patients with advanced papillary renal cell carcinoma: Data from the German prospective RCC-Registry

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Background: Because renal cell carcinoma (RCC) is diagnosed 75-80% with clear cell histology, there is little data on treatment and outcome of patients (pts) with non-clear RCC. They are reported to have a poorer prognosis and are often excluded from clinical trials. Here, we present data on papillary RCC, the most common non-clear cell subtype (10-15% of RCC).

Methods: The prospective German RCC-Registry includes pts with advanced or metastatic RCC at start of systemic first-line therapy. Data on patient and tumour characteristics, all systemic therapies and outcome are collected. More than 300 medical and uro oncologists are recruiting pts since 2007.

Results: Median age for pts with papillary RCC (n = 92) at start of first-line therapy was 66 years. According to MSKCC risk category, pts were classified into 30% low, 55% intermediate and 2% high risk (12% unknown). From 2007 to May 2016 (data cut) treatment changed. First-line, the use of sunitinib declined and the use of temsirolimus and pazopanib increased. Since 2011 (n = 46), first-line treatments included 33% (n = 15) temsirolimus, 30% (n = 14) sunitinib and 22% (n = 10) pazopanib. The most frequently used second-line treatments since 2011 (n = 28) are sunitinib (36%, n = 10), everolimus and pazopanib (18%, n = 5 each), temsirolimus (11%, n = 3) followed by axitinib and sorafenib (7%, n = 2, each). The most frequently used first -> second-line strategies (first-line since 2011, n = 23) are mTor inhibitors (temsirolimus) -> TKI (35%, n = 8) and TKI -> TKI (26%, n = 6) (TKI: sunitinib, axitinib, pazopanib or sorafenib). Updated data (data cut May 2017) including nivolumab will be presented. Median progression-free survival (PFS) for the first-line was 6.1 months (95% CI 4.0 - 9.9) for pts with papillary RCC versus (vs) 8.6 (7.7 - 9.7) for pts with clear cell RCC (ccRCC, n = 772). For the second-line, median PFS was 3.7 (2.3 – 4.9) vs 4.8 (4.2 – 5.8) (papillary vs ccRCC). Median overall survival (OS) was 12.7 (8.5 – 23.8) vs 20.8 (19.1 – 23.8) (papillary vs ccRCC).

Conclusions: We show first- and second-line treatment of pts with advanced papillary RCC. Our data indicate that prognosis for pts with papillary RCC might be inferior to that of pts with clear cell RCC.

Clinical trial identification: NCT00610012

Legal entity responsible for the study: iOMEDICO AG

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910P Exome sequencing of tumor samples from S1107 "Randomized phase II evaluation of tivantinib and tivantinib in combination with erlotinib in patients with papillary renal cell carcinoma (pRCC)"

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Background: pRCC is associated with activation of MET pathway, overexpression of EGFR and inferior responses to VEGF inhibition than clear cell RCC. In S1107 we randomized patients (pts) with advanced pRCC and 0-1 prior systemic therapy to MET inhibitor tivantinib at 360 mg BID (Arm 1) or tivantinib 360 mg BID plus EGFR inhibitor erlotinib at 150 mg daily (Arm 2). 66% of pts had no prior systemic therapy; 6% had type 1 pRCC, 42% had type 2, and 52% had no subtype assigned. The study was closed at interim analysis after 55 pts were enrolled and 0% RR was noted. Median PFS was 2.0 and 3.3 months, and OS was 10.3 and 11.3 months in Arms 1 and 2 respectively. These results were inferior to previously reported clinical trials with pRCC. To better understand these outcomes we performed whole exome sequencing of tumor samples collected from pts participating in this study.

Methods: Exome of 16 pts were successfully sequenced using Agilent SureSelect probes. The mean coverage of target regions ranged from 45x to 91x. Only reads aligned to unique genomic location were retained. The single point mutations and small indels were identified using GATK HaplotypeCaller. Copy number analysis was performed using Bioconductor package "DNACopy" and customized R scripts.

Results: Most of the mutations were unique to individual pts indicating high diversity of variants in this patient cohort. Only 1 MET mutation was ascertained affecting tyrosine kinase domain (K1198I). Other mutations associated primarily with type 2 pRCC included CDKN2A, PBRM1, SETD2, KDM6A, FAT1, NF2, CUL. No EGFR and FH mutations were detected. The most affected pathways included WNT, cadherin and mitotic G2-G2/M phase. Somatic copy number variation was challenging to obtain since no matching normal tissues were collected, but MET amplification was suspected in minority of cases.

Conclusions: S1107 patient cohort had a high proportion of pts with molecular subtypes not driven by MET abnormalities and would not be expected to respond well to MET inhibition. Although MET remains a reasonable therapeutic target in pRCC, careful selection of pts exhibiting MET alterations is required to better benefit from therapy with MET inhibitors.

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Legal entity responsible for the study: Southwest Oncology Group

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911P Patients (pts) with metastatic non-clear cell renal cell carcinoma (mnccRCC) treated with Nivolumab (Nivo) based immunotherapy as advanced treatment (ATL) line: analysis of a national early access program (EAP)

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Background: Immunotherapy with the andi-PD1 Nivo is a standard ATL for clear cell mRCC. Data on its activity in the rare variant of mnccRCC is limited (case reports). We aimed to report the activity of Nivo in mnccRCC pts treated per a national EAP.

Methods: Records from consecutive mnccRCC pts treated with Nivo ATL per a national EAP in 6 centers were retrospectively reviewed. We report the clinical benefit, progression free survival (PFS), overall survival (OS), and toxicity.

Results: Between 7/2015 – 12/2016, 16 mnccRCC pts (median age 64, male 68%; papillary type 38%, n = 6; chromophobe 44%, n = 7; undifferentiated 12%, n = 2; pure sarcomatoid 6%, n = 1). 62% (n = 10) were treated with second line Nivo, and 38% (n = 6) as third and fourth line. Heng risk was good/intermediated/poor in 6% (n = 1)/ 75% (n = 12)/19% (n = 3). Clinical benefit (stable disease+ partial response) was 37% (4 partial response and 2 stable disease). Median PFS was 3.5 months (mos). After a median follow up time of 8 mos, 100% of the pts with a clinical benefit are still with a benefit and on treatment (range 5-18m). Most pts (69%, n = 11) are alive, with median OS not reached. Toxicity was mild grade 1-2 in the majority of pts (56%, n = 9).

Conclusions: Nivo as ATL may be active in mnccRCC pts, and associated with durable responses and predictable mild toxicity. Future and larger studies are needed to assess the activity of immunotherapy in this uncommon type of mRCC.

Legal entity responsible for the study: the author

Funding: None

Disclosure: All authors have declared no conflicts of interest.

912P Cabozantinib for the treatment of patients with metastatic variant histology renal cell carcinoma (vhRCC): a retrospective study

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Background: Cabozantinib (C) prolongs overall survival (OS) and progression-free survival (PFS) in patients with metastatic clear-cell renal cell carcinoma (ccRCC) that progressed on first-line VEGFR-TKI. No standard of care systemic therapy exists for the management of patients with metastatic vhRCC.

Methods: This is a retrospective, IRB approved study of patients with vhRCC who received cabozantinib at MD Anderson Cancer Center from January 2014-January 2017. Information collected from the medical records included the baseline characteristics, toxicity, dose reductions, and OS. A blinded radiologist assessed the radiographic response using RECIST v1.1. Descriptive statistics, the Kaplan Meier method and the log rank test were applied using Microsoft Excel and GraphPad Prism version 6 software.

Results:

Table: 912P

	N = 30
Gender	Male = 26 (86.7%)
Age, median (range)	58.4 years (25-81)
Prior Nephrectomy	27 (90%)
Histology	Papillary (P) 17 Chromophobe (Chr) 6 Other: unclassified 3, translocation 2, sarcomatoid (sarc) 1, mucinous tubular/spindle cell 1
Prognostic Risk Group MSKCC IMDC	Good/Intermediate/Poor 2/20/8 2/ 23/5
Number of Prior Therapies 0 1 >1 Median (range) Previous VEGFR Tyrosine Kinase Inhibitor	3 7 20 2 (0-5) 26

Median PFS was 8.6 months (mos) (95%CI: 6.1-14.7), and median OS was 22.7 mos (95%CI:10.8-NR), median follow up 10.6 months (95%CI: 7.1-14.1). There were no significant differences detected between patients with papillary versus non-papillary histologies with respect to PFS or OS. At last follow up, 13 patients remain on treatment with median time on therapy for all patients of 15.0 months. Of the 28 patients with measurable disease, there were 4 confirmed PRs (2 P, 1 Chr, 1 unclassifed) for a 14% ORR. For the entire cohort, 20 of 30 (66.7%) with stable disease, and 6 of 30 with progressive disease (20%), for a disease control rate of 24 of 30 (80%). Of 21 patients who started C at 60 mg/d, 12 (57%) required dose reduction due to toxicity. Multiple patients required treatment breaks but none discontinued therapy due to toxicity.

Conclusions: In this retrospective study, C produced a clinically meaningful benefit in patients with metastatic vhRCC, the majority of whom had PD on prior VEGFR-TKIs. Prospective trials of C in vhRCC are warranted and planned.

Legal entity responsible for the study: Matthew T Campbell

Funding: None

Disclosure: M.T. Campbell: Serve on advisory boards for Eisai and AstraZeneca. M.A. Bilen: Advisory board for Exelixis. N. Tannir: Served as a consultant and has served on advisory board for Exelixis. All other authors have declared no conflicts of interest.

913P Avelumab in patients with metastatic adrenocortical carcinoma (mACC): Results from the JAVELIN solid tumor trial

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Background: Avelumab is a human anti–PD-L1 IgG1 antibody that has shown promising clinical activity in multiple tumor types, and is approved in the US for the treatment of metastatic Merkel cell carcinoma. Here, we report an updated analysis of avelumab in patients (pts) with mACC, representing the largest prospective monotherapy study performed to date in this rare cancer with limited therapeutic options.

Methods: In a phase 1b cohort (NCT01772004), pts with mACC and prior platinum-based therapy received avelumab at 10 mg/kg IV Q2W until progression, unacceptable toxicity, or withdrawal. Prior and ongoing treatment with mitotane was permitted. Tumors were assessed every 6 wks (RECIST v1.1). Endpoints included safety (NCI-CTCAE v4.0), best overall response, objective response rate (ORR), progression-free survival (PFS), and overall survival (OS).

Results: As of Dec 31, 2016, 50 pts from 6 countries received avelumab for a median of 3.4 mos (0.5–24.8). Median follow-up was 16.5 mos (11.7-27.6); 5 pts (10.0%) remained on treatment. Median age was 50 y (range 21–71) and median time since diagnosis of metastatic disease was 14.5 mos. 24 pts (48.0%) had received ≥2 prior lines of treatment for advanced disease (median 1, range 0–6). 41 pts (82.0%) had a treatment-related adverse event (TRAE) of any grade; the most common (>15%) were nausea (20.0%) and fatigue (18.0%). 8 pts (16.0%) had a grade ≥3 TRAE, of which only increased ALT (4.0%) occurred in > 1 pt. 12 pts (24.0%) had an immune-related AE of any grade. Confirmed ORR was 6.0% (3 partial responses; 95% CI 1.3–16.5); response was ongoing in 1 pt at data cutoff. 21 pts (42.0%) had stable disease as best response (disease control rate 48.0%). Median PFS was 2.6 mos (95% CI 1.4–4.0). Median OS was 10.6 mos (95% CI 7.4–not estimable) and the 12-mo OS rate was 47.0% (95% CI 31.8–60.9). Responses occurred in 2 pts with PD-L1+ tumors and 1 PD-L1 − (≥5% tumor cell cutoff). In PD-L1 + (n = 12) vs PD-L1 − (n = 30) subgroups, median PFS was 5.5 vs 1.7 mos (HR 0.66; 95% CI 0.3–1.4) and median OS was 14.4 vs 11.5 mos (HR 0.82; 95% CI 0.3–2.2), respectively.

Conclusions: Avelumab had a manageable safety profile and demonstrated clinical activity in pts with platinum-treated mACC.

Clinical trial identification: NCT: NCT01772004 Protocol: EMR 100070-001

Legal entity responsible for the study: Pfizer Inc., New York, NY, USA; Merck KGaA, Darmstadt, Germany.

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Disclosure: C. Le Tourneau: Provided a consulting role for MSD, Bristol-Myers Squib, Novartis and AstraZaneca and received honoraria from Merck Serono and AstraZaneca. C. Zarwan: Provided an advisory role for Revere Pharmaceutics and consulting for Perceptive Informatics. C. Hoimes: Provided an advisory role for Seattle Genetics and Eisai, and participated in speaker's bureau's for Bristol-Myers Squib and Genentech. D.J. Wong: Received research funding from Armo Biosciences, BioMed Valley Discoveries, Roche-Genentech, Merck, EMD Serono, Bristol-Meyers Squibb, KURA Oncology, AstraZeneca. Provided an advisory role for Bristol-Meyers Squibb. S. Bauer: Research support: Novartis, Blueprint Medicines, Ariad; Consultant: GSK, Novartis, Pfizer, Bayer, Fresenius, Lilly, Blueprint Medicines, Deciphera; Honoraria (CME): Pharmamar, GSK, Pfizer, Bayer; Travel support: Pharmamar, Bayer. M. Wermke: Received research funding from Novartis, Pfizer, Roche, Novartis, Roche, Boehringer Ingelheim and Celgene. Provided an advisory role for Roche, Novartis, Bristol-Myers Squib, AstraZeneca and received honoraria from Roche, Novartis, Boehringer Ingelheim. H.J. Grote: Employee of Merck KGaA, Darmstadt, Germany. A. von Heydebreck: Employee of Merck KGaA, Darmstadt, Germany and holds Merck KGaA, Darmstadt, Germany stock. K. Chin: Employee of EMD Serono Inc. All other authors have declared no conflicts of interest.

914P Do patients (pts) with advanced nonseminomatous germ cell tumors (aNSGCT) and unfavorable time to normalization (TTN) of tumor markers benefit with prolongation of 1-st line chemotherapy (ChT)?

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Background: Three-four cycles of BEP are commonly recognized as a standard 1-st line ChT in aNSGCT. However, there were no trials studying optimal cycles numbers in this setting, especially in case of unfavorable TTN of tumor markers. We performed retrospective single center analysis to evaluate if pts with unfavorable TTN of tumor markers may benefit with prolongation of induction ChT.

Methods: Inclusion criteria were as follows: (1) ChT-naïve aNSGCT pts treated with etoposide- and cisplatin-based chemotherapy; (2) AFP and hCG levels available at days 0 and 18-22 of cycle 1 to calculate TTN (Fizazi K., JCO 2004). Pts who received less than "standard" number of cycles (3xBEP or 4xEP for IGCCCG good risk, 4xBEP for intermediate and poor risk) for any reason were excluded from the analysis. Cox regression multivariate analysis was also performed. TTN was calculated by K.Fizazi's methodic (JCO 2004).

Results: From 1987 to 2011 952 pts with aNSGCT received 1-st line ChT. 584 pts matched the inclusion criteria. Unfavorable TTN had 24 (11%), 61 (41%) and 122 (84%) of pts with good, intermediate and poor IGCCCG risk, respectively. More than standard number of cycles received 199 pts. Prolongation of ChT did not result in significant improvement of OS in any IGCCCG prognostic groups irrespectively of TTN (Table).

Table: 914P

IGCCCG risk group	TTN/# of cycles	N pts	5-y OS, %	p (HR, 95%CI)
Good	favorable/standard	176	92%	0,44
	favorable/>standard	42	98%	(HR 0,63, 0,23-1,89)
	unfavorable/standard	15	93%	0,65
	unfavorable/> standard	9	78%	(HR 1,48, 0.24-10.48)
Intermediate	favorable/standard	127	88%	0,14
	favorable/>standard	20	80%	(HR 2,1, 0,73-9,38)
	unfavorable/standard	32	81%	0,66
	unfavorable/> standard	29	86%	(HR 0,78, 0.25-2.41)
Poor	favorable/standard	12	91%	0,17
	favorable/>standard	10	100%	(HR 0,14, 0.01-2.27)
	unfavorable/standard	23	65%	0,55
	unfavorable/> standard	89	72%	(HR 0,79, 0.33-1.79)

Conclusions: Prolongation of 1-st line ChT beyond standard number of cycles does not improve outcome of pts with unfavorable TTN of tumor markers.

Legal entity responsible for the study: Alexey Tryakin

Funding: None

Disclosure: All authors have declared no conflicts of interest.

915P The prognostic role of neutrophil-to-lymphocyte ratio (NLR) in patients with metastatic germ cell tumors

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Background: NLR is a robust prognostic factor in many solid tumors. Limited data exist about its role in patients with metastatic germ cell tumors (GCTs).

Methods: We utilized a single institution database of patients diagnosed with metastatic GCTs between January 1990 and December 2013 who were treated with chemotherapy at Princess Margaret Cancer Centre. The peripheral blood count prior to first line chemotherapy was used to calculate the derived NLR (absolute neutrophil count divided by the total white blood cell count minus the absolute neutrophil count). Predictive accuracy was assessed as the association between NLR and overall survival and was evaluated using a Cox proportional hazard model adjusted for the International Germ Cell Cancer Collaborative Group (IGCCCG) risk classification. Discriminatory accuracy was evaluated by determining the area under the receiver operating characteristic curve (AUROC) for survival at 5 years. The optimal cut-off for NLR selection was chosen based on a highest AUROC.

Results: In total, 475 patients were identified of which NLR data were available from 354 (75%) patients. Among these, 63% were good risk, 23% intermediate risk and 15% poor risk. The 5-year survival for good, intermediate and poor risk groups was 96.3%, 92.4% and 62.9%, while 10-year survival was 94.8%, 92.4% and 62.9%, respectively. Over the whole cohort, a NLR cut-off of 2.5 provided the best discriminatory accuracy with an AUROC of 0.70 (95% CI 0.59-0.75, $p < 0.001$). In a univariable analysis, NLR >2.5 was associated with a hazard ratio (HR) of 3.91 (95% CI 2.01-7.60, $p < 0.001$) which persisted after adjustment for IGCCCG risk group (HR 2.33, 95% CI 1.14-4.76, $p = 0.02$). Among patients with IGCCCG high risk, 5-year survival was 87.5% if NLR $\leq$ 2.5, whilst if NLR $>$ 2.5, 5-year survival was only 51.3%.

Conclusions: A high NLR is associated with an adverse survival in patients with metastatic GCTs undergoing first line chemotherapy and provides moderate discriminatory accuracy in this setting. The utility of NLR appears particularly marked in patients with IGCCCG high risk disease.

Legal entity responsible for the study: Senior authors, Dr. Jeremy Lewin and Dr. Eitan Amir

Funding: None

Disclosure: All authors have declared no conflicts of interest.

916P Biological assessment of viable germ cell tumor (VT) in patients (pts) with seminoma (S) and non-seminoma (S) using miR371

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Background: The pathological constitution of residual nodes after chemotherapy or of the borderline enlarged retroperitoneal (RP) lymph nodes in clinical stage I (CSI) germ cell tumor (GCT) pts on surveillance is challenging, especially in tumor markers (TM) negative pts. Currently, accurate assessment requires pathological confirmation with RPLND or clinical follow-up to establish a pattern of growth. A plasma-based approach to identify patients with VT would be uniquely valuable.

Methods: Formalin-fixed paraffin embedded (FFPE) and plasma from GCTs patients were used for miRNAs extraction. Non-cancer FFPE testicular tissue and plasma from healthy volunteers were used as negative controls. miR371 expression was detected by RT-PCR and relative expression calculated by the 2-ΔΔCt method. miR-93-5p was used as positive internal control. Results were analyzed for associations with clinicopathologic features using Fisher's exact test.

Results: miR371 was over-expressed in all the primary testicular ($n = 4$) and mediastinal ($n = 3$) samples while it was undetectable in the atrophic testis ($n = 1$) and mediastinal or gonadal teratoma ($n = 2$), confirming the applicability of the technique to the FFPE samples. 21 metastatic samples were analyzed: 2 lung, 1 brain, 17 lymph nodes and 1 IVC tumor thrombus. The samples were collected prior to ($n = 2$) or after ($n = 12$) chemotherapy, while 7 pts were treated only with surgery. miR371 was undetectable in any samples (0/9) with no VT on pathological examination and over-expressed in 11/12 (91.6%) of those with viable GCT (OR 145.7; $p < 0.0001$). 90% of pts with positive miR-371 had negative TM (100% of S and 75% of NS) while no pts with negative miR-371 had positive TM. Plasma miR-371 also showed high correlation with VT (Table).

Table: 916P

Pts	Initial stage	Stage at the suspicious relapse	Histology	miR71	Evidence of VT
1	I	IIA	S	+	+ (RPLND)
2	I	IIA	S	–	– (negative PET scan)
3	I	IIA	S	–	– (regressing CT scan)
4	I	IIA	NS	+	+ (progressing CT scan)

Conclusions: Elevated plasma levels of miR-371 correlate with the presence of active germ cell malignancy. These encouraging findings suggest that plasma miR371 levels may lead to biological rather than radiographic assessment of the presence of active GCT in patients with S and NS.

Legal entity responsible for the study: Lucia Nappi

Funding: None

Disclosure: All authors have declared no conflicts of interest.

917P A single centre retrospective review of testosterone deficiency in germ cell cancer patients

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Background: Testosterone deficiency syndrome (TDS) is frequently described in men treated for germ cell cancer with rates quoted between 11 and 38% (Huddart et al 2005). Observational studies show that TDS reduces quality of life and carries cardiovascular, metabolic and bone health risks. At our institute we observed that men with symptoms of TDS and 'low normal' testosterone (T) (8.6 – 12 nmol/L) were not reliably recognised.

Methods: We collected retrospective data from all germ cell cancer referrals to the Bristol Cancer Institute from 2011 – 2016. We documented age, treatment, at least one random T level within a year of diagnosis (grouped into < 8, 8 – 12 and > 12 nmol/L), details of symptoms and treatment of TDS.

Results: Data was collected on 462 patients (36 excluded with non germ cell diagnoses and 26 excluded due to T never being measured). Median age was 36 years (range 17 – 89) with 85% of patients aged under 50. 58% of men had seminoma, 32% non-seminoma and 10% combined germ cell cancer. 41% of all patients had a T level $<$ 12 nmol/L at first measurement (32% of 20 – 29 year olds, 42% of 30 – 49 and 58% of 50 – 59 year olds) and 16% had T $<$ 8 nmol/L. T therapy was prescribed in 19% of patients. Men receiving adjuvant carboplatin had the highest rate of T therapy (23%) compared with patients on surveillance (18%) and BEP or EP chemotherapy (14%).

Conclusions: In this retrospective series 41% of patients had at least one total T value $<$12 nmol/L. 19% received replacement. A TDS diagnosis should not be based on a single measurement but regardless of age, once T falls to $<$ 15 nmol/L, severity of TDS sequelae correlate with further decline (Morgentaler et al 2016). There is a range of what is regarded as normal T and it declines naturally with age. Recognition and management of late effects is important in men with curable cancer and diagnosis must be individualised; addressing symptoms alongside biochemical parameters. This is reflected by germ cell cancer social media websites where men frequently describe serum T in the defined normal range with symptoms of TDS. Further prospective multicentre studies could better define the prevalence of TDS in these patients and be used to inform a standard diagnostic approach.

Legal entity responsible for the study: Jeremy Braybrooke

Funding: None

Disclosure: All authors have declared no conflicts of interest.

918TiP Pembrolizumab and nanoparticle albumin bound paclitaxel (nab-paclitaxel) for metastatic urothelial carcinoma (UC) after chemotherapy failure: the open-label, single-arm, phase 2 PEANUT study

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Background: Pembrolizumab (pembro) is a new standard of care in chemotherapy (CT) pre-treated UC patients (pts) and nab-paclitaxel (nPtx) has shown one of the highest activities among CT options in UC. Their combination may overcome resistance to immunotherapy (IT) and result in longer delay in the time to disease progression (PD). We will explore dynamic biomarkers of response to CT+IT.

Trial design: In an open-label, single-arm, single-center, phase 2 trial, pts receive pembro 200 mg intravenously (IV) on D1 and nPtx at the dose of 125 mg/m^2 IV on D1 and D8. Cycles are repeated every 3 weeks until PD or onset of unacceptable toxicity. Key inclusion criteria are: predominant UC, failure of $\leq$ 2 platinum-based CT for metastatic disease (2nd-to-3rd line only). Neoadjuvant/adjuvant CT is counted if relapse occurred $\leq$6 months of the last CT cycle. Response is evaluated by RECIST criteria v.1.1 every 2 cycles. PD-L1 expression will be assessed at the study conclusion on both immune cells (IC) and tumor cells at a centralized laboratory (Qualtek, Goleta, CA, USA). The primary endpoint of the study is the progression-free survival (PFS). The target is to detect an improvement in the median PFS from $\leq$3.0 months (H0) to $\geq$ 5.0 months (H1). To achieve 90% power with a one-sided non-parametric test at the 10% significance level,

we estimated that 64 pts must be accrued over 18 months, with follow-up duration of 12 months. PFS will be also analyzed according to the PD-L1 expression. Should the above investigation suggest that the treatment benefit is stronger in PD-L1+ pts, there is the option to expand this cohort up to a maximum of 50 pts. As such, we estimate 85.1% power to detect the target improvement in PFS. The decision of cohort expansion will rely on predictive power (PP) calculation: a PP $\geq$ 30% will be regarded as promising. Translational analyses will include multiparametric flow cytometry of blood samples, gene expression (RNA-seq, Illumina HiSeq) and mutation profiling of tumor samples (Ion Torrent Personal Genome Machine). These profiles will be matched with response to treatment and PFS/overall survival (EudraCT number 2017-000579-10).

Clinical trial identification: EudraCT number 2017-000579-10

Legal entity responsible for the study: Fondazione IRCCS Istituto Nazionale dei Tumori

Funding: Merck

Disclosure: All authors have declared no conflicts of interest.

919TiP Pembrolizumab ± chemotherapy versus chemotherapy in advanced urothelial cancer: Phase 3 KEYNOTE-361 trial

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Background: Inhibitors of programmed death 1 (PD-1) and its ligand PD-L1 are effective for treatment of recurrent, advanced urothelial cancer. Data from KEYNOTE-052 showed first-line pembrolizumab (anti–PD-1) had antitumor activity with an acceptable safety profile in cisplatin-ineligible patients (pts) with advanced urothelial cancer. This suggests pembrolizumab may be effective as first-line treatment, a setting in which only 50% of pts can receive the current standard-of-care, cisplatin-based chemotherapy. A randomized, open-label, phase 3 study in pts with advanced urothelial carcinoma is assessing first-line pembrolizumab ± chemotherapy versus chemotherapy (KEYNOTE-361; NCT02853305).

Trial design: Approximately 990 pts with histologically or cytologically confirmed unresectable/metastatic urothelial carcinoma will be randomly assigned 1:1:1 to pembrolizumab 200 mg every 3 weeks (Q3W), pembrolizumab + chemotherapy (investigator's choice of cisplatin [70 mg/m^2 Q3W] plus gemcitabine [1000 mg/m^2 on days 1 and 8 Q3W] OR carboplatin [AUC 5 Q3W] plus gemcitabine if cisplatin ineligible), or chemotherapy alone. Pts must have measurable disease per investigator review (RECIST v1.1), an ECOG PS 0–2, received no prior systemic chemotherapy for advanced urothelial cancer, and provided a tumor biopsy. Treatment allocation will be stratified by chemotherapy (cisplatin or carboplatin) and PD-L1 expression (+ or –). Patients will be treated for 35 cycles of pembrolizumab (pembrolizumab arms only), or until progressive disease or unacceptable adverse events. The primary end points are progression-free survival (RECIST v1.1 per blinded independent central review) and overall survival, assessed in all patients and PD-L1+ patients. Secondary end points are objective response rate and safety. Efficacy will be compared for pembrolizumab versus chemotherapy and pembrolizumab + chemotherapy versus chemotherapy. Patient accrual is ongoing; 1 interim efficacy analysis is planned.

Clinical trial identification: NCT02853305; July 29, 2016

Legal entity responsible for the study: Merck & Co., Inc.

Funding: Merck & Co., Inc.

Disclosure: T. Powles: Received research funding from Merck, AstraZeneca and Roche; honoraria and travel expense reimbursement from Pfizer, Merck, AstraZeneca, Roche, and Novartis. J.E. Gschwend: Served as advisor for and received honoraria and reimbursements for travel expenses from Bayer, Bristol-Myers Squibb, Janssen, Novartis, Pfizer, and Roche. Y. Loriot: Served as advisory board member for Astellas, Janssen, Roche, MSD, AstraZeneca; received research funding and honoraria from Sanofi and received reimbursement for travel expenses from Roche, MSD, Janssen, and AstraZeneca. J. Bellmunt: Received honoraria from Merck, Genentech, Pfizer, and AstraZeneca. C. Vulsteke: Served as consultant/advisor to Novartis, Leo Pharma, and Roche and received reimbursement for travel expenses from Novartis, Pfizer, and Roche. M. Abdelsalam: Have been an advisory board member for Pfizer, Merck, Novartis, served on speakers' bureaus for Pfizer and Roche, received honoraria from Pfizer, Merck, Roche, Novartis, AstraZeneca, and been reimbursed for travel expenses by Amgen, Roche, AstraZeneca. M. Fleming: Served as advisory board member and as speakers' bureau member for Genentech. M. Markus: Served as consultant/advisor for Biotheranostics. D. Feng: Employed by and own stock in Merck & Co., Inc. C. Poehlein: Employed by Merck & Co., Inc. A. Alva: Received honoraria from and served as consultant/advisor to Eisai and have received research funding from BIND Biosciences, Bristol-Myers Squibb, Genentech, Novartis, and Oncogenex. All other authors have declared no conflicts of interest.

920TiP Afatinib in patients with advanced or metastatic urothelial carcinoma (UC) with genetic alterations in ErbB receptors 1–3 who failed on platinum-based chemotherapy: The Phase II LUX-Bladder 1 trial

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Background: First-line treatment of patients (pts) with advanced or metastatic UC consists of platinum-based chemotherapy (CT), and currently, there is no well-established therapy following CT failure. Recently, checkpoint inhibitors have shown clinical benefit in this setting, and are likely to become a future standard of care. However, to date, no other targeted therapies have shown significant clinical activity. Given that ~20% of UCs harbour ERBB receptor alterations or abnormalities, the blockade of the ERBB pathway may be an effective therapeutic strategy. Indeed, afatinib, an irreversible ERBB family blocker, demonstrated activity in a Phase II trial in a subgroup of pts with UC harbouring ERBB2/ERBB3 aberrations. These data provide rationale for the current Phase II trial assessing afatinib in pts with UC, molecularly selected for ERBB receptor alterations (LUX-Bladder 1; NCT02780687).

Trial design: The Phase II, single-arm LUX-Bladder 1 trial evaluates the efficacy and safety of afatinib in pts with UC and ERBB2/ERBB3 mutations or ERBB2 amplification (Cohort A), or EGFR amplification (Cohort B). Eligible pts are $\geq$18 years of age, with histologically confirmed advanced/metastatic UC of the urinary tract not amenable to surgery and progression during or after platinum-based CT (previous immunotherapy allowed), ECOG PS 0–1, with archival tissue samples available for pre-screening biomarker analysis. Pts will receive oral afatinib 40 mg/day until disease progression or discontinuation for other reasons. Cohort A will enrol in two stages, with Stage (S) 2 enrolment depending on afatinib anti-tumour activity in S1. The primary endpoint and key secondary endpoint in Cohort A are PFS rate at 6 months and ORR; other secondary endpoints include PFS, OS, disease control rate, duration of response and tumour shrinkage. These endpoints will also be explored in Cohort B. Safety and biomarkers will be assessed in both cohorts. The trial commenced in June 2016. Recruitment is ongoing in Spain and planned in two additional European countries; planned enrolment: Cohort A, ~70 pts (S1, n=~25; S2, n=~45); Cohort B, ~10 pts.

Clinical trial identification: NCT02780687; 1200.261

Legal entity responsible for the study: Boehringer Ingelheim

Funding: Boehringer Ingelheim

Disclosure: J. Puente: Consulting/advisory role: Pfizer, Roche, Janssen, Lilly Speakers bureau: Pfizer, BI, Astellas Research funding: Astellas, Pfizer. F.J. Vazquez Mazon: Honoraria: Janssen/Astellas/Sanofi/Bayer/Novartis Consulting/ad board/Expert testimony: Janssen Astellas/Sanofi/Bayer/Novartis; Speaker: Novartis; Travel, accommodations, expenses: Astellas/Pfizer/Janssen. N. Sala: Consulting/advisory role: Astellas, Janssen, Pfizer, Bristol-Myers Squib; Speakers bureau: Astellas, Janssen, Pfizer, Bristol-Myers Squib; Travel, accommodations, expenses: Astellas, Pfizer, Janssen. E. Grande Pulido: Research funding: Astellas, Pfizer, AstraZeneca. D. Castellano: Honoraria: Pfizer, Astellas, Janssen; Consulting/advisory role: Roche, Epsen; Speakers bureau: Amgen, Novartis, Bristol-Myers Squib. M.A. Climent: Honoraria: Roche, Bristol-Myers Squib, Bayer, Astellas, Sanofi, Janssen, Pfizer, Novartis; Consulting/advisory role: Janssen, Pfizer, Roche, Sanofi, Astellas, Bayer; Travel, accommodation, expenses: Astellas, Janssen, Pfizer. P. Jares: Patents, royalities, other intellectual property: Barcelona University. I. Aldecoa: Travel, accommodation, expenses: Sysplex Espana S.L. N. Gibson, J. Serra, E.R. Imedio, E. Ehrnrooth: Employment: BI. All other authors have declared no conflicts of interest.

921TiP A Phase III, randomized, double-blind, multicenter study of adjuvant nivolumab vs placebo in patients (pts) with high-risk invasive urothelial carcinoma (UC; CheckMate 274)

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Background: Standard of care for muscle-invasive bladder cancer (predominant form of UC) is cisplatin-based neoadjuvant chemotherapy followed by radical cystectomy + pelvic node dissection or cystectomy + pelvic node dissection alone if cisplatin-ineligible. Some pts undergo surgical resection followed by adjuvant cisplatin-based chemotherapy. Many pts are not candidates for adjuvant chemotherapy or are not treated due to lack of proven survival benefit. UC of the ureter or renal pelvis is typically managed with nephroureterectomy. Despite surgery ± chemotherapy, pts with invasive UC are at high risk of recurrence and death. Based on the efficacy and safety of the programmed death-1 (PD-1) inhibitor nivolumab for metastatic or unresectable UC progressing despite chemotherapy (CheckMate 032 and 275), we are conducting an international phase III study of adjuvant nivolumab vs placebo in pts with invasive UC (originating in bladder, ureter, or renal pelvis) following resection (NCT02632409).

Trial design: Pts must have had radical surgical resection ± cisplatin-based neoadjuvant chemotherapy within the past 120 days and be disease-free (by imaging) ≤4 weeks before randomization. Pts who did not receive cisplatin-based neoadjuvant chemotherapy must be ineligible for or refuse adjuvant cisplatin. Tumor tissue must be provided for biomarker analysis. Pts are ineligible if they had partial cystectomy or partial nephrectomy, or secondary treatment after surgical removal of UC (eg, cisplatin-based adjuvant chemotherapy), prior malignancy within 3 years except those treated with curative intent and in remission, or any condition requiring systemic treatment with immunosuppressants (eg, corticosteroids) within 2 weeks of treatment. Recruitment began in February 2016; target enrollment is ∼640 pts. Co-primary endpoints: Disease-free survival (defined as the time between date of randomization and date of first recurrence or death) in pts with tumors expressing ≥1% PD-ligand 1 and in all randomized pts. Secondary endpoints: Non-urothelial tract recurrence-free survival, disease-specific survival, overall survival.

Clinical trial identification: NCT02632409

Legal entity responsible for the study: Bristol-Myers Squibb

Funding: Bristol-Myers Squibb

Disclosure: D. Bajorin: Reports grants from Bristol-Myers Squibb, during the conduct of the study; other from Bristol-Myers Squibb, outside the submitted work. M.D. Galsky: Consultant for Astellas, AstraZeneca, Genentech, Merck, Novartis and hold stock options for Dual Therapeutics. Y. Tomita: Received honoraria from Novartis and Pfizer, have been a consultant for Novartis and Ono, and have received research funding for Astellas, AstraZeneca, Pfizer, and Takeda. A. Azrilevich: Employee for Bristol-Myers Squibb, the sponsor of this study. Salaried and did not receive any particular payment for participation in this abstract. All other authors have declared no conflicts of interest.

922TiP KEYNOTE-564: Phase 3 trial of pembrolizumab in the adjuvant treatment of renal cell carcinoma (RCC)

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Background: Effective adjuvant therapies for patients (pts) with RCC at risk of recurrence after nephrectomy are lacking. Programmed death ligand 1 (PD-L1) and 2 (PD-L2) expression predicts poor prognosis in RCC. Programmed death 1 (PD-1) inhibitors have demonstrated activity in metastatic RCC, and PD-1 may represent a novel therapeutic target in the adjuvant setting. Pembrolizumab is a PD-1 inhibitor that directly blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2. This randomized, double-blind, placebo-controlled phase 3 trial will evaluate the efficacy and tolerability of pembrolizumab as adjuvant therapy in pts with RCC who have T2 grade 4, T3, T4, N (+), or stage M1 with no evidence of disease (M1 NED) following nephrectomy and/or metastasectomy (NCT03142334).

Trial design: Key inclusion criteria are: age ≥18 years; histologically confirmed RCC with a clear cell component; intermediate-high or high risk of recurrence, or M1 NED; no prior systemic therapy for advanced RCC; disease-free following complete or partial nephrectomy (and metastasectomy in M1 NED pts) with negative surgical margins; and Eastern Cooperative Oncology Group (ECOG) performance status 0-1. Approximately 950 pts will be randomly assigned in a 1:1 ratio to receive pembrolizumab 200 mg every 3 weeks by intravenous infusion, or placebo, continued for up to 17 cycles (∼1 year) or until disease recurrence or treatment discontinuation. Randomization will be stratified by metastasis stage (M0 vs M1 NED); within the M0 group, randomization will be further stratified by ECOG performance status (0 vs 1) and region (US vs rest of world). The primary end point is investigator-assessed disease-free survival (DFS). Radiographic imaging will be performed every 12 weeks. Secondary objectives include overall survival (OS), safety, disease recurrence-specific survival, DFS and OS according to PD-L1 expression status, pharmacokinetics, anti-drug antibodies, and patient-reported outcomes. Molecular biomarkers that may be associated with response, safety, pharmacodynamic activity, or mechanism of action will be evaluated as exploratory objectives.

Clinical trial identification: NCT03142334; May 3, 2017

Legal entity responsible for the study: Merck & Co., Inc.

Funding: Merck & Co., Inc.

Disclosure: T.K. Choueiri: Ad Board and/or funding: AstraZeneca Bayer Bristol-Myers Squib Cerulean Eisai, Foundation Medicine Inc Genetech, GlaxoSmithKline, Merck, Novartis, Peloton, Pfizer, Prometheus Labs Inc, Roche, Eisai Exelixis GSK Merck, Tracon. T. Powles: Research Funding/Honoraria/Travel: Pfizer, Merck, AstraZeneca, Roche, Novartis T. Zhang: Owns stock in Capio Biosciences and have received research funding from Janssen, Pfizer, and Acerta. D.I. Quinn: Ad board/funding/honoraria: Pfizer, Bristol-Myers Squib, Merck, EMD Serono, AstraZeneca, Genentech, Exelixis. J.E. Gschwend: Ad board/Honoraria/Travel Expenses: Bayer, Bristol-Myers Squib, Janssen, Novartis, Pfizer, Roche. S.S. Wan: Employment and stock ownership: Merck & Co., Inc. C. Poehlein: Employment: Merck & Co/MSD.

923TiP A phase 2 BIOmarker driven trial with Nivolumab and Ipilimumab or VEGFR tKi in naïve metastatic Kidney cancer: the BIONIKK trial

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Background: Nine targeted agents have been approved for metastatic clear cell renal cell carcinoma (mccRCC) in the last 10 years, including VEGFR-tyrosine kinase inhibitors (TKI), mTOR inhibitors and checkpoint inhibitor (CI). Combination of CI nivolumab and ipilimumab is currently compared to sunitinib in a randomised phase III trial in first-line setting. While treatment opportunities of mccRCC are moving rapidly biomarker to select patients to receive TKI or CI are still lacking. Based on transcriptomic analysis, we have defined four distinct molecular groups (ccrcc1 to 4) in patients with mccRCC treated with sunitinib. These groups were mainly characterized by distinct responses to suntinib as well as distinct immune cell compositions and inhibitory receptor expressions.

Trial design: The proof of concept study BIONIKK is a French multicentric randomised phase II designed to assess the use of molecular groups to select treatment in first-line mccRCC. Molecular group is determined on frozen tumor sample within 2 weeks. Treatment is then allocated between TKI and nivolumab plus ipilimumab for ccrcc2 and 3 and between nivolumab alone and nivolumab plus ipilimumab for ccrcc1 and 4. Main objective is to assess efficacy of each treatment arm according to molecular group. Primary endpoint is overall response rate using RECIST 1.1. Main secondary endpoints include PFS, OS and their relationship to exploratory biomarkers. These latter include protein and gene expression analyses of tumor microenvironment (TME) from formalin-fixed and paraffin-embedded tumor samples. In addition, phenotype and functional status of peripheral blood lymphocytes will be analysed with flow cytometry before and during treatment. A Bayesian model was used to avoid independent analyses of the effect of drugs using hierarchical borrowing. Bionikk is not designed to be conclusive on the superiority of any treatment but will generate important hypotheses on putative biomarkers to select patients to receive TKI, CI alone or in combination. From this point of view, Bionikk is the first biomarker-driven trial in first line metastatic ccRCC.

Clinical trial identification: NCT02960906 First received: August 18, 2016

Legal entity responsible for the study: Association Pour La Recherche des Thérapeutiques Innovantes en Cancérologie

Funding: Association Pour La Recherche des Thérapeutiques Innovantes en Cancérologie and Bristol-Myers Squibb

Disclosure: S. Oudard: Honorarium fees from Astellas, Pfizer, Sanofi, Janssen, Bristol-Myers Squibb. Y-A. Vano: Honorarium fees from Bristol-Myers Squibb, Pfizer, Novartis, Astellas, Sanofi, Janssen, Roche. All other authors have declared no conflicts of interest.

924TiP Savolitinib versus sunitinib in patients with MET-driven, unresectable and locally advanced or metastatic papillary renal cell carcinoma: SAVOIR, a randomised, phase III trial

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Background: Papillary renal cell carcinoma (PRCC) is the most common of the non-clear cell renal cell carcinomas (RCCs), accounting for 10–15% of RCCs. However, there are no therapies approved specifically for patients with PRCC, who currently receive treatments approved for clear cell RCC, such as sunitinib. PRCC is often MET-driven (defined as *MET* kinase domain mutations, *MET* amplification, chromosome 7 gain and/or *HGF* amplification). Savolitinib (AZD6094, HMPL-504, volitinib) is a highly selective MET tyrosine kinase inhibitor which demonstrated anti-tumour activity for patients with MET-driven PRCC in a phase II trial.

Trial design: SAVOIR (NCT03091192) is a global, phase III, open-label, randomised, controlled trial evaluating the efficacy and safety of savolitinib, compared with sunitinib, in patients with MET-driven, unresectable, locally advanced or metastatic PRCC. Approximately 180 patients will be randomised at ~50–75 sites across 5–10 countries. Eligible patients (aged ≥18 with MET-driven PRCC confirmed by a novel, sponsor designated, validated, targeted next-generation sequencing assay; a Karnofsky performance status ≥80; and measurable disease at baseline) will be randomised in a 1:1 ratio to receive either continuous savolitinib 600 mg (400 mg if < 50 kg) orally, once daily (QD), or sunitinib 50 mg orally QD (4 weeks on/2 weeks off). The primary objective is to determine the efficacy of savolitinib compared with sunitinib in terms of progression free survival (PFS). Tumour assessments (RECIST 1.1, confirmed by blinded independent central review [BICR]) will be performed at screening and the end of every 6-week cycle until 12 months, and every 12 weeks thereafter until disease progression. Secondary endpoints include overall survival, objective response rate, duration of response, best percentage change in tumour size, disease control rate at 6 and 12 months, safety and tolerability, and biomarkers. The impact of savolitinib compared with sunitinib on disease symptoms and quality of life, along with the pharmacokinetics of savolitinib will also be assessed.

Clinical trial identification: Clinical trial registration number: NCT03091192

Legal entity responsible for the study: AstraZeneca

Funding: AstraZeneca

Disclosure: T.K. Choueiri: Ad boards: AstraZeneca, Bayer, Bristol-Myers Squib, Cerulean, Eisai, Foundation Med. Inc., Genetech, GSK, Merck, Novartis, Peloton, Pfizer, Prometheus Labs, Roche, Eisai; Funding: AstraZeneca, Bristol-Myers Squib, Exelixis, Genentech, GSK, Merck, Novartis, Peloton, Pfizer, Roche, Tracon, Eisai; Travel. R. Jakacki, M.M. Frigault, L. Ottesen: Employed by AstraZeneca. D. Ghiorghiu, V. Haddad, A. Kohlmann: Employee and shareholder- AstraZeneca

925TiP A phase 2 study of investigational TORC1/2 inhibitor TAK-228 and TAK-228 plus investigational PI3Kα-selective inhibitor TAK-117 vs everolimus in adults with advanced or metastatic clear-cell renal cell carcinoma (ccRCC) that has progressed on VEGF-targeted therapy

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Background: VEGF-targeted therapies are the cornerstone of first and subsequent lines of therapy in ccRCC; however, resistance develops almost invariably. Another proven therapeutic intervention in ccRCC is treatment with the allosteric mTOR inhibitor everolimus, which only partially inhibits TORC1 and thus results in increased phosphorylation of Akt and paradoxical hyperactive signalling. TAK-228, a highly selective ATP-competitive TORC1 and TORC2 inhibitor, has shown promising antitumor activity and acceptable safety in ccRCC. In a pooled analysis of 2 prior studies of 41 patients (pts) with ccRCC, TAK-228 treatment resulted in 1 CR, 5 PR and 21 pts with SD; 13 pts who achieved ≥SD had prior treatment with a rapalog. The median duration of overall response was 250 d (range, 55–1614). The most common AEs were fatigue, nausea and hyperglycemia. Also, combination of TAK-228 with TAK-117, a selective inhibitor of PI3Kα, has shown more complete and prolonged inhibition of TORC1 and TORC2. This phase 2, open-label, randomized study will evaluate the efficacy and safety of TAK-228 and TAK-228+TAK-117 vs everolimus in pts with advanced or metastatic ccRCC that have progressed on or after VEGF-targeted therapy (NCT02724020).

Trial design: 189 pts will be randomized 1:1:1 to TAK-228 30 mg once-weekly on d1, 8, 15, 22 with a light meal; TAK-228 4 mg once-daily (QD) + TAK-117 200 mg QD on d1–3, 8–10, 15–17, 22–24 on an empty stomach; or everolimus 10 mg QD, in 28-d cycles. Pts will be stratified by number of prior therapy lines and IMDC risk category. Pts with histologically confirmed advanced/metastatic ccRCC, ≥1 prior line of VEGF-targeted therapy with PD, KPS ≥70%, and adequate organ function, but no CNS metastasis or prior therapy with agents that target PI3K, AKT, or mTOR are eligible. Pts in the everolimus arm who progress may crossover. An interim futility analysis will be conducted after 30 pts in each arm have received 2 treatment cycles. Primary endpoint is PFS. Secondary endpoints are OS, TTP, ORR, CBR, safety, and QoL. As of January 24, 2017, 54 pts have been screened.

Clinical trial identification: NCT02724020

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: T.K. Choueiri: Advisory board member: AstraZeneca, Bayer, BMS, Cerulean, Eisai, Foundation Medicine Inc., Genetech, GlaxoSmithKline, Merck, Novartis, Peloton, Pfizer, Prometheus Labs Inc, Roche, Eisai; Research funding: AstraZeneca, BMS, Exelixis, Genentech, GSK, Merck, Novartis, Peloton, Pfizer, Roche, Tracon, Eisai (all institutional); Travel expenses, including accommodations: for advisory boards C. Porta: Consultant and/or Speaker for Novartis, Bristol-Myers Squib, Ipsen, Pfizer, Jannsen, Eisai, EUSA, Peloton; received research grant from Pfizer. R. Alter: Advisory boards: Astellas, Teva Speakers bureau: AstraZeneca, Astellas, Eisai, Novartis, Sanofi, Merck, Pfizer, Janssen, Bayer, Exelixis, Amgen, Bristol-Myers Squibb, Genetech. I. Duran: Consulting/Advisory role: Roche/Genentech, Ipsen, Sanofi, Bristol-Myers Squib, MSD, Janssen. Ad board: Roche/Genentech, Ipsen. Travel/accommodation/expenses: Astellas, Janssen, Roche/Genentech. Research funding: Astellas, Roche/Genentech. C. Patel: Employment: Takeda Pharmaceuticals, Inc. Stock/ownership: Takeda Pharmaceuticals, Inc. Patents/royalties: Takeda Pharmaceuticals, Inc. Travel/accommodation/expenses: Takeda Pharmaceuticals, Inc. R. Neuwirth, A. Enke: Employment: Millennium Pharmaceuticals, Inc. F. Zohren: Employment: Takeda Pharmaceuticals, Inc. T. Powles: Research funding: AstraZeneca, Roche. Honoraria: Roche, AstraZeneca, Bristol-Myers Squib, Novartis, Pfizer. All other authors have declared no conflicts of interest.

926TiP Phase Ib/II trial of interleukin-2 (IL-2) and nivolumab in metastatic clear cell renal cell cancer (RCC)

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Background: High dose Interleukin-2 (HD IL2) immunotherapy is standard therapy in suitable patients (pts) with metastatic clear cell RCC who have good performance status. HD IL-2 is unique among RCC therapies in eliciting durable complete responses (DCR) with a median duration of such responses of 12 years. However, the complete response (CR) proportion for HD IL-2 monotherapy is only 7-9%. There is an urgent need to evaluate HD IL2 combination therapies that could increase the response proportion. IL-2 promotes early steps in the lymphocyte activation cascade, increases trafficking of cytotoxic T lymphocytes to the tumor and induces Th1 differentiation of CD4 T helper cells. Nivolumab, an immune checkpoint inhibitor, blocks the interaction between PD-1 on activated T cells and its ligands that are expressed on immune cells and tumor cells. We hypothesize that the combination of HD IL2 and a PD-1 inhibitor would elicit a potent synergistic anti-cancer immune response reflected in improved response proportion and survival with acceptable toxicity in pts with metastatic clear cell RCC.

Trial design: This multi-site Ib/II trial will determine safety and efficacy of HD IL-2 in combination with nivolumab for RCC. Pts with metastatic clear cell RCC, 0-2 prior systemic therapies and candidates for HD IL2 and for nivolumab are eligible. Pts will be treated with HD IL-2 (600,000 IU/kg/dose every 8 hours for up to 14 doses) on Days 1-5 and again on Days 15-19, with nivolumab (240 mg IV every 14 days) starting on Day 8 +/- 3 wks. Pts will continue on nivolumab every 2 wks for up to 48 wks barring intolerable toxicities or consent withdrawal or progressive disease. Nivolumab may potentially be continued beyond first progression. The primary objective/endpoint of the phase 1b portion of the trial is safety of the combination/immune mediated grade 3/4 events of interest. The primary endpoint of the phase II portion of the trial is the overall response proportion (ORR) as assessed by RECIST 1.1. Secondary endpoints are safety/toxicity, overall survival and PFS at 2 years. Planned accrual is 23 evaluable subjects over 2 years. Whole blood and serum will be analyzed for circulating immune cell repertoire and baseline tumor tissue will be sequenced.

Clinical trial identification: NCT02989714

Legal entity responsible for the study: Ajjai Alva

Funding: Prometheus, University of Michigan

Disclosure: A. Alva: Advisory role for Eisai, AstraZeneca and Roche. Received research funding: Genentech, Novartis, Bristol-Myers Squib, BIND Bioscience, Acerta Pharma, Merck, Prometheus Laboratories, Covance, Mirati Therapeutics, United Biosources Corporation, ARIAD, Pfizer & Bayer. All other authors have declared no conflicts of interest.

927TiP Cabozantinib in patients with advanced penile squamous cell carcinoma (PSCC): the open-label, single-arm, single-center, phase 2, CaboPen trial

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Background: Chemotherapy (ChT) exerts moderate activity in advanced and metastatic PSCC, and efficacy outcomes are poor. Neoadjuvant treatment is a reliable setting to address activity of new drug approach (Necchi A et al. ASCO-GU 2017). The vascular endothelial growth factor (VEGF) receptor is overexpressed in approximately 50% of PSCC. Cabozantinib (Cabo) is a multiple receptor tyrosine kinase inhibitor (TKI) primarily targeting MET and VEGFR2.

Trial design: In an open-label, single-arm, single-center, phase 2 trial, patients (pts) with clinical stage N2-3 (TNM 2009, locally-advanced [LA]) or M1 PSCC will receive Cabo, orally, at a dose of 60 mg/day continuously until surgery, evidence of disease progression or onset of unacceptable toxicity. Prior ChT administration is not allowed. Response will be evaluated by RECIST criteria v.1.1, matched with 18FDG-PET/CT assessment, every 2 months. At each time of disease restaging, responding pts with LA PSCC who will be considered eligible to radical lymphadenectomy will undergo surgery. After surgery, pts will be managed according to standard guidelines. The primary endpoint (EP) is the objective response-rate (ORR=CR+PR according to RECIST v1.1). Secondary EP are safety, progression-free survival (PFS) and overall survival (OS), and pathologic response. The study is planned according to Simon's Optimal two-stage design, with H1=20% and H0= 5%, and type I and type II error rates set at the 10% level. In stage 1, 12 evaluable pts will be accrued. If 1 pt at least will be responding, enrolment will be extended to the 2nd stage for further 25 pts. If, out of the total of 37 pts, 4 at least will be responding, treatment will be declared worthy for further investigations. Stopping rules based on the Bayesian posterior probability (PP) to demonstrate that the ORR exceeded 20% are set. Translational analyses on pre- and post-Cabo tumor samples and matched blood samples will include *in-situ* hybridization for HPV and next generation sequencing (Ion Torrent Personal Genome Machine). These profiles will be associated with response to treatment and PFS/OS (EudraCT number 2017-001963-19).

Clinical trial identification: EudraCT number 2017-001963-19

Legal entity responsible for the study: Fondazione IRCCS Istituto Nazionale dei Tumori

Funding: Ipsen

Disclosure: All authors have declared no conflicts of interest.

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GYNAECOLOGICAL CANCERS

930O Quality of life in patients with recurrent ovarian cancer (OC) treated with niraparib: Results from the ENGOT-OV16/NOVA Trial

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Background: The highly selective poly(ADP-ribose) polymerase (PARP) 1/2 inhibitor niraparib (ZEJULA™) concentrated in the tumor vs plasma in preclinical studies, delivering ≥90% durable PARP inhibition, and showed significantly longer progression-free survival vs placebo in patients (pts) with recurrent OC following complete (CR) or partial response (PR) to platinum-based chemotherapy (PBC) regardless of germline *BRCA* mutation (g*BRCA*mut) or homologous recombination deficiency (HRD) status in the phase 3 ENGOT-OV16/NOVA trial. Quality of life (QoL) measures are important to determine the benefit of drug therapy in this population. We evaluated patient-reported outcomes (PROs) associated with QoL and individual patient-reported symptoms using the Functional Assessment of Cancer Therapy-Ovarian Symptoms Index (FOSI) and European Quality of Life Scale 5-Dimensions (EQ-5D-5L) in ENGOT-OV16/NOVA pts treated with niraparib vs placebo.

Methods: A mixed-effects growth-curve model adjusted for baseline demographic values and 3 stratification factors was constructed to model the relationship between treatment and PRO score for each measure. The relationship between health status and PROs was evaluated through a cross-sectional analysis of adjusted EQ-5D-5L health utility index (HUI) scores. A disutility analysis of hematologic adverse events was conducted at different time points.

Results: No significant difference in mean PRO scores was observed between niraparib and placebo arms in either cohort. Adjusted HUI scores were similar in both arms at baseline, but average adjusted HUI pre-progression scores trended higher in the niraparib arm (0.812 vs 0.803 in g*BRCA*mut cohort; 0.845 vs 0.828 in non-g*BRCA*mut cohort). Hematologic toxicities had no detrimental effect on pts' overall health utility.

Conclusions: These data suggest pts with recurrent OC treated with niraparib following CR or PR to PBC can continuously maintain their QoL while on treatment.

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Legal entity responsible for the study: TESARO, Inc.

Funding: TESARO, Inc.

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931O A phase IIa study of tisotumab vedotin (HuMax®-TF-ADC) in patients with relapsed, recurrent and/or metastatic cervical cancer

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Background: There are limited therapeutic options available for patients (pts) with relapsed, recurrent, and/or metastatic cervical cancer. Historic data indicate dismal outcome with ORR of 0-15% and a median OS of 6-8 months (Mo). Tisotumab vedotin (Tv) is an antibody-drug conjugate (ADC) composed of a Tissue Factor specific human IgG1 monoclonal antibody conjugated to a microtubule disrupting agent Monomethyl Auristatin E (MMAE) and is being tested in an ongoing Ph I/IIa dose-escalation study (NCT02001623) in pts with locally advanced and/or metastatic solid tumors. Here, we present initial data on the pre-planned 30 pt expansion cohort in relapsed, recurrent, or metastatic cervical cancer.

Methods: Key eligibility criteria included recurrent or metastatic cervical cancer with at least 1 prior line of therapy, adequate liver and kidney function and ECOG 0-1. Tv was given as 2 mg/kg q3w until progression. Efficacy and toxicity were assessed according to RECIST 1.1 and CTCAE 4.03.

Results: Thirty pts were enrolled. Median age was 43 (21-73), median prior lines 2 (1-5). Twenty-nine pts had previously received cisplatin, 28 a taxane and 19 also bevacizumab. Preliminary efficacy data for 19 pts were available at time of submission. Ten pts (33%) experienced Gr 3 TEAE(s) related to GI (2 pts), anemia (2 pts), infections (1 pt), neuropathy (1 pt), bleeding (1 pt), other (7 pts). No Gr 4 or 5 AEs were reported. The toxicity profile appeared to be consistent with MMAE-based ADCs, including peripheral neuropathy and neutropenia with an identified compound-specific toxicity of conjunctivitis for which prophylactic management was introduced. Seven of the 19 pts (37%) evaluable for efficacy obtained a clinical response; hereof, 6 were confirmed at time of submission. With a mean follow-up of 5.5 Mo for the 7 responders, 5 remain on trial with none of the responders having relapsed. Full efficacy data for all 30 pts will be available at time of presentation.

Conclusions: Preliminary data demonstrated a manageable safety profile and encouraging efficacy (ORR 37%) in relapsed, recurrent or metastatic cervical cancer. Our findings in a high unmet medical need population warrant further investigation.

Clinical trial identification: NCT02001623, released November 14, 2013

Legal entity responsible for the study: Genmab A/S

Funding: Genmab A/S

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Pfizer, Sanofi, Taiho a.o. M. Johnson: Lilly Serono Kadmon Janssen Mirati Therapeutics Genmab Pfizer AstraZeneca Genentech/Roche Novartis Checkpoint Therapeutics Array BioPharma Regeneron Abbvie Merrimack Tarveda Astellas, Otsuka, Genentech/Roche, Boehringer-Ingelheim. S. Lisby, L. Basse: Employed by Genmab and hold shares in the company. R. Coleman: Member of Genmab's Advisory Board for Tisotumab vedotin. D.S. Hong: Research/Grant Funding: Bayer, Lilly, Genentech, LOXO, Pfizer, Amgen, Mirati, Ignyta, Merck, Daichi-Sanko, Eisai; Travel, Accommodations, Expenses: MiRNA, LOXO; Consulting Role: Bayer, Baxter, Guidepoint Global Other: Oncoreseponse (founder). All other authors have declared no conflicts of interest.

932PD Efficacy of olaparib maintenance therapy in patients (pts) with platinum-sensitive relapsed ovarian cancer (PSROC) by lines of prior chemotherapy: Phase III SOLO2 trial (ENGOT Ov-21)

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Background: In the Phase III SOLO2 trial (NCT01874353), maintenance treatment with the poly(ADP-ribose) polymerase inhibitor olaparib (Lynparza) was shown to significantly improve progression-free survival (PFS) vs placebo in pts with PSROC and a *BRCA1/2* mutation (*BRCA*m; hazard ratio [HR] 0.30, 95% CI 0.22–0.41; $P<0.0001$; median 19.1 vs 5.5 months; Pujade-Lauraine *et al.* SGO 2017). A previous retrospective analysis of data pooled from 6 studies of olaparib in pts with a germline *BRCA*m suggested that olaparib activity declined as the number of prior lines of chemotherapy received increased (Matulonis *et al. Ann Onc* 2016). We report an analysis of PFS in SOLO2, grouped by number of prior lines of platinum-based chemotherapy (PBC) received by pts, performed to identify the most appropriate use of olaparib in the maintenance setting.

Methods: SOLO2 enrolled pts who had received ≥2 prior lines of PBC before being in response to their most recent regimen. Pts were randomized 2:1 to receive olaparib tablets (300 mg bid) or placebo. PFS was investigator assessed with modified RECIST v1.1. For the PFS subgroup analyses, subgroups were predefined; HRs were calculated using a Cox proportional hazards model.

Results: Of 295 randomized pts, 195 received olaparib and 99 received placebo. 85 pts in the olaparib arm (43.4%) had received ≥3 prior lines vs 37 pts (37.4%) in the placebo arm. Pts who had received 2 prior lines of PBC were more likely to have had a platinum-free interval of > 12 months (70.9% vs 48.3% and 40.0% for 3 and ≥4 prior lines, respectively in the olaparib arm; 69.4% vs 60.0% and 23.5% placebo) and a complete response at baseline (50.9% vs 36.7% and 48.0% olaparib; 54.8% vs 35.0% and 35.3% placebo) vs pts who had received ≥3 prior lines.

Conclusions: In SOLO2, olaparib maintenance monotherapy improved PFS in pts with PSROC irrespective of the number of prior lines of PBC received.

Clinical trial identification: NCT01874353, 1 June 2017

Legal entity responsible for the study: AstraZeneca

Funding: AstraZeneca

Disclosure: R. Penson: Honoraria: Amgen, Genentech, AstraZeneca, Endocyte, Eisai, Vascular Biogenics, Baxalta, AbbVie, Clovis, Tesaro; research: Genentech, ImClone, Endocyte, AstraZeneca, Eisai, Amgen, Vascular Biogenics; commercial: Advance Medical. J. Ledermann: Honoraria from AstraZeneca and Pfizer, and consulting fees from AstraZeneca, Clovis Oncology, Pfizer and Roche. M. Friedlander: Research grants and advisory board honoraria from AstraZeneca. N. Colombo: Reports grants and personal fees from AstraZeneca, and personal fees from Roche, Pharmamar, Clovis, Pfizer and Tesaro. M. Gropp-Meier: Honoraria from AstraZeneca. G.S. Sonke: Institutional research funding by AstraZeneca, Merck, Novartis and Roche. A. Allen: Employee of AstraZeneca. E. Pujade-Lauraine: Received advisory board membership and honoraria from AstraZeneca and Pfizer, and advisory board membership, honoraria and speakers' bureau membership from Roche. All other authors have declared no conflicts of interest.

933PD The exposure-response relationship of niraparib in patients with gBRCAmut and non-gBRCAmut: Results from the ENGOT-OV16/NOVA Trial

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Background: Niraparib (ZEJULA™) is a selective PARP1/2 inhibitor approved for maintenance treatment of adults with recurrent ovarian cancer who are in a complete or partial response to platinum-based chemotherapy. In preclinical studies, niraparib concentrates in the tumor versus plasma, delivering ≥90% durable PARP1/2 inhibition and a persistent antitumor effect. We report the relationship between exposure and response of niraparib in patients (pts) enrolled in the ENGOT-OV16/NOVA trial.

Methods: Preliminary modeling for niraparib was performed using Phase 1 study data (N = 104) to identify the initial parameters for the pharmacokinetic model, which was developed using combined Phase 1 and Phase 3 data (N = 512 pts) and the first-order conditional estimation with interaction method within NONMEM. Exposure-efficacy relationships were evaluated in the g*BRCA*mut and non-g*BRCA*mut cohorts separately;

Table 932PD: PFS subgroup analysis by number of prior lines of PBC received

	Prior lines of PBC received					
	2		3		≥4	
	Olaparib	Placebo	Olaparib	Placebo	Olaparib	Placebo
n*	110	62	60	20	25	17
PFS events,† n (%)	57 (51.8)	44 (71.0)	34 (56.7)	19 (95.0)	16 (64.0)	17 (100)
Median PFS, months	22.1	5.7	16.9	5.1	17.0	5.4
Hazard ratio (95% CI)	0.38 (0.26–0.57)		0.24 (0.13–0.42)		0.26 (0.13–0.51)	

*Number of prior lines of PBC was unknown for one olaparib-arm patient;
†Progression or death by modified RECIST v1.1

the efficacy was compared in pts with high exposure (> median exposure) vs low exposure (≤ median exposure). Maximum plasma concentration (C_{max}) and area under the curve over the dosing interval (AUC_{tau}) at steady state (SS) were the exposure metrics. Progression-free survival (PFS) was used as efficacy endpoint. Hazard ratios (HRs) and 95% confidence intervals (CI) for the low and high niraparib exposure groups in each cohort were provided, with exposure group as the independent variable and PFS as the dependent variable. Exposure and safety data of g*BRCA*mut and non-g*BRCA*mut cohorts were combined to evaluate exposure-safety relationships using logistic regression.

Results: In the g*BRCA*mut cohort, the HR was 0.91 (95% CI, 0.54-1.52) for niraparib exposure as measured by the SS AUC_{tau} for pts in the high exposure vs. the low exposure group. In the g*BRCA*mut cohort, the HR was 0.70 (95% CI, 0.49-0.99). Logistic regression analysis did not show any significant relationship between the incidence of thrombocytopenia or anemia Grade ≥ 3 and the SS Cmax or AUC increase.

Conclusions: Observed exposure-response relationships support the selection of 300 mg as the starting dose in both g*BRCA*mut and non-g*BRCA*mut pt populations. A trend towards increased efficacy associated with increased exposure was observed in the non-g*BRCA*mut cohort.

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Legal entity responsible for the study: TESARO, Inc.

Funding: TESARO, Inc.

Disclosure: J. Wang, Z-Y. Zhang, X. Wang, S. Agarwal: Employment: Tesaro Stock: Tesaro. M.R. Mirza: Consulting or Advisory Role: Roche, Clovis Oncology, AstraZeneca, Tesaro. L. Gilbert: Honoraria: AstraZeneca, Advaxis Consulting/Advisory Role: AstraZeneca, Advaxis. A.V. Tinker: Consulting/Advisory: AstraZeneca. J.S. Berek: Consulting/Advisory: Atara Biotherapeutics. H.S. Pentikis, V. Kansra: Advisory board or board of directors: Tesaro Consulting: Tesaro. B. Benigno: Honoraria: AstraZeneca, Insys Therapeutics Research funding: Tesaro. S.J. Hazard: Employment: Tesaro, Genentech/Roche Stock: Tesaro, Genentech/Roche Travel, Accommodations, Expenses: Tesaro, Genentech/Roche. B.J. Rimel: Consulting/Advisory Role: AstraZeneca, Tesaro, Genentech/Roche Honoraria: Genentech. U.A. Matulonis: Consulting/Advisory: Merck KGaA, AstraZeneca, Immunogen, Tesaro, Genentech. All other authors have declared no conflicts of interest.

934PD Safety and Efficacy of Niraparib in Elderly Patients (Pts) with Recurrent Ovarian Cancer (OC)

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Background: Niraparib (Zejula™) is a selective poly(ADP-ribose) polymerase 1/2 inhibitor (PARPi) approved for maintenance therapy in adults with recurrent OC who are in response to platinum-based therapy. Here, we report safety and efficacy of niraparib in the subgroup of pts from the ENGOT-OV16/NOVA trial who were aged ≥65 years (y).

Methods: Pts were assigned to one of two independent cohorts based on germline BRCA mutation (gBRCAmut) status and randomized 2:1 within each cohort to receive either niraparib (300 mg) or placebo once daily. Pts were stratified by age (<65 vs ≥ 65 y) to analyze efficacy (measured by progression-free survival [PFS]) and safety. Efficacy and safety were also tested in patients <70 vs ≥ 70 y.

Results: Efficacy of niraparib was comparable in pts <65 vs ≥ 65 y in both gBRCAmut and non-gBRCAmut cohorts (Table). Efficacy was also similar in pts <70 vs ≥ 70 y in both cohorts (gBRCAmut: <70 y, HR = 0.30; ≥70 y, HR = 0.09. Non-gBRCAmut: <70 y, HR = 0.47; ≥70 y, HR = 0.35), although the sample size of pts who were ≥70 y in the gBRCAmut cohort was small (14 niraparib vs 7 placebo). The most common adverse events (AEs; nausea, constipation, fatigue, hypertension, anemia, thrombocytopenia, neutropenia) in the niraparib arm occurred with similar incidence in pts <65 vs ≥ 65 y as well as in pts <70 vs ≥ 70 y. Grade 3/4 AEs occurring in > 10% of niraparib-treated pts were consistent in pts <65 vs ≥ 65 y (thrombocytopenia, 27% vs 31%; anemia, 27% vs 20%; neutropenia, 12% vs 10%) and in pts <70 vs ≥ 70 y (thrombocytopenia, 28% vs 31%; anemia, 27% vs 13%; neutropenia, 11% vs 10%, respectively). There were no Grade 5 events.

Table: 934PD

Cohort	Patient Numbers		PFS Hazard Ratio (95% Confidence Interval)
	Niraparib	Placebo	
gBRCAmut			
<65 y	110	49	0.27 (0.16, 0.44)
≥65 y	28	16	0.27 (0.09, 0.81)
Non-gBRCAmut			
<65 y	130	69	0.54 (0.37, 0.80)
≥65 y	104	47	0.38 (0.23, 0.61)

Conclusions: Niraparib was safe and highly effective in elderly patients.

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Legal entity responsible for the study: TESARO, Inc.

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935PD BRCA1&2 tumoral and germline status for ovarian cancer patients in first line setting within the PAOLA-01 trial

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Background: PAOLA-01 is a randomized placebo-controlled, international phase III study, assessing olaparib in maintenance therapy in advanced high grade ovarian carcinoma patients responding to 1st line platinum-taxane-based chemotherapy plus bevacizumab. Stratification is performed on treatment outcome and on tumoral *BRCA1/2*

status (tBRCA) at screening. As secondary objective, the consistency between germline (gBRCA) and tBRCA testing is being explored.

Methods: This study is planned to recruit 762 pts in Europe and 24 in Japan. tBRCA is tested on FFPE tumor block within 5 French national institutional platforms using 2 different next-generation sequencing methods based either on capture or on re-sequencing technology. For French pts, gBRCA testing is performed in parallel in the same platforms.

Results: Since May 2015, 1181 pts have been screened and 662 pts randomized. tBRCA status was assessed in 962 samples with a median turn around time of 40 days (range 8-260). Only 44(4.6%) tumor samples were non-informative (too low tumor cellularity), 8 using capture method and 36 by re sequencing respectively. A deleterious variant (DV) was reported in 279 (29%) samples (191 (68%) in *BRCA1*, 87 (31%) in *BRCA2* and one in both genes). Twelve variants of unknown significance were identified for *BRCA2* and 13 for *BRCA1*. For the 384 French pts, where both gBRCA & tBCRA testing was performed in parallel we report the mutation rate detection in the Table below. Of note, only one large genomic rearrangement of *BRCA1* was detected in blood sample exclusively.

Conclusions: tBRCA testing is a reliable tool for clinical trials with acceptable delay for clinical practice. Proportion of tBRCA testing failure is low and consistency with germ line testing adequate for routine practice.

Table: 935PD

French Cohort	gBRCA + (%)	gBRCA-(%)	Total (%)
tBRCA +	67 (17)	23 (6)	90 (24)
tBRCA -	1 (0.3)	270 (70)	271 (71)
Inconclusive tumor testing	1 (0.3)	22 (5,7)	23 (6)
total	69 (18)	315 (82)	384 (100)

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936PD Actionable molecular alterations in advanced gynecologic malignancies: First results from the ProfiLER program (NCT01774409) in France

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Background: Despite progresses in precision medicine, very few molecularly-targeted agents (MTA) are available for gynecologic cancer patients (pts). Objectives were to characterize tumor genomic alterations in the gynecological subpopulation of the ProfiLER program, to identify actionable alterations and to report clinical efficacy of MTA if used outside approved indications.

Methods: The ProfiLER program is a multicentric prospective trial to implement molecular profiling in pts with advanced disease. All potential pts with advanced gynecologic cancers were eligible. DNA extracted from either archival or fresh collected tumor samples was analyzed by targeted exon sequencing (NGS) of 59 cancer related genes and whole genome array comparative genomic hybridization (CGH). Genomic profiles were presented in a dedicated molecular tumor board (MTB) for recommendation of MTA when applicable.

Results: Out of the 2184 included pts in the ProfiLER program, 242 pts with advanced gynecologic cancer were recruited from March 2013 to April 2016. For 211 (87%) pts (ovary, n = 136; cervix, n = 22; uterus, n = 45; others, n = 8), molecular analyses have been performed (median delay 2.8 months). 101 pts (48%) had at least one actionable alteration: PIK3CA (n = 23), KRAS (n = 10), ERRB2 (n = 9) and 50 other alterations. 109 MTA were recommended in 83 pts: PI3K/AKT/mTOR inhibitors (n = 46), sorafenib (n = 19), lapatinib (n = 7) and 17 other MTA (n = 37). 54 pts have not received MTA at the time of the analysis (poor PS or death, n = 25; stable disease, n = 15; no dedicated clinical trial, n = 7; other, n = 7). Currently, 29 pts initiated MTA. Partial response was reported for 8 pts (28%) and a stable disease at 3 months for 6 pts (21%). 12 pts (41%) progressed and 3 were non-evaluable. Median progression-free survival was 2.7 months (95% CI 1.9-5.4). Median overall survival was 64.8 months (38-101) for pts receiving MTA and 49.8 months (39-63) for pts not receiving MTA.

Conclusions: CGH and NGS identified actionable alterations on 48% of pts with gynecologic cancer and are feasible in routine practice. Nearly half of patients treated derived benefit from the recommended MTA, but these represent a minority of the whole screened population.

Clinical trial identification: NCT01774409

Legal entity responsible for the study: Prof. Jean-Yves Blay, Centre Léon Bérard, Lyon (France)

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937PD PD-L1 expression and prognosis significance in advanced ovarian cancer

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Background: Recent data suggest that programmed death ligand 1 (PD-L1) expression may predict response to anti–programmed death 1 (PD-1) therapy. This retrospective observational study evaluated the prognostic effect of PD-L1+ expression in patients with histologically confirmed epithelial ovarian, primary peritoneal, or fallopian tube cancer (OCa).

Methods: Patients diagnosed with FIGO stages II-IV OCa from 2004-2012, at Aarhus University Hospital and Rigshospitalet, Copenhagen, Denmark, were included. PD-L1 expression was measured in tissue collected at OCa surgery, using immunohistochemistry with anti–PD-L1 22C3 antibody. PD-L1$^+$ expression was defined as staining in $\geq$ 1% of tumor or inflammatory cells. Patients partially sensitive (PPS; treatment-free interval [TFI] of 6-12 mo) or fully sensitive (FPS; TFI >12 mo) to platinum therapy were considered platinum sensitive, whereas those refractory (TFI <3 mo) or resistant (TFI of 3-6 mo) to platinum were platinum insensitive. Data were analyzed using Cox proportional hazard model, adjusting for age, stage, histology, residual tumor, surgery type, performance status, and/or TFI.

Results: Median age of the 376 patients at diagnosis was 63 years (range, 26-86). 77% had histologic grade 2/3 serous adenocarcinoma, 46% had residual tumor after surgery, and 9%, 70%, and 21% had FIGO stages II, III, and IV disease, respectively. FPS, PPS, platinum-resistant, and platinum-refractory disease comprised 49%, 27%, 15%, and 9% of patients, respectively. 50.5% of patients were PD-L1$^+$, with prevalence increasing with increased platinum sensitivity (P for linear trend <0.05). Median overall survival (OS) was 43 mo (50.4 mo in PD-L1$^+$ vs 38.3 mo in PD-L1$^-$ patients). A statistically significant association was seen between PD-L1$^+$ tumors and longer OS (adjusted hazard ratio [aHR], 0.71 [95% CI, 0.55-0.91]). The association was not significant in platinum-insensitive patients (aHR, 0.82 [0.50-1.36]), but there was a tendency towards significance in platinum-sensitive patients (0.77 [0.57-1.06]), driven by those with a TFI of 6-12 mo.

Conclusions: PD-L1 was frequently expressed in advanced OCa patients, and expression may be prognostic, particularly in those with partially platinum-sensitive OCa.

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938PD Prognostic relevance of immune-related gene expression signatures (irGES) in patients (pts) with ovarian clear cell carcinomas (OCCC)

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Background: Little is known about the immune microenvironment of OCCCs and its impact on outcomes. We studied the expression of a panel of immune response genes in OCCC to identify the presence and prognostic relevance of irGES in these tumours.

Methods: Immune response gene profiling was performed on 84 FFPE OCCC samples with matched clinical outcomes, collected between 2003 – 2016, using the nanoString nCounter PanCancer Immune Profiling Panel. Unsupervised hierarchical clustering analysis was performed and each sample underwent analysis for protein levels of PD-1, PD-L1, MMR and ARID1A via immunohistochemistry (IHC).

Results: Total of 74/84 samples were successfully profiled. Median age at diagnosis was 53 yrs. 41 (55.4%) were stage 1, 7 (9.5%) stage 2, 24 (32.4%) Stage3, 2 (2.7%) stage 4. 64/74 (86.5%) of pts received adjuvant chemotherapy post debulking surgery with 38% recurrence rate (median PFS 27 months (m)). Median follow up was 36m. Based on irGES, 4 distinct molecular subgroups of OCCCs were identified. G1 was hallmarked by high NK cell markers/PD-1 expression, G2 by increased CTLA-4/PD-L1 expression, G3 by adhesion cell markers, and G4 by increased levels of pro - angiogenic genes. G1 was observed to have significantly poorer PFS (median PFS 20m vs 68m, p= 0.011) and a trend towards poorer OS when compared with G2/3/4 (median OS 38.8m vs undefined, $p = 0.0501$). G4 carried the best prognosis (median PFS 108m vs 26m, p= 0.0515; median OS undefined, p= 0.0726). This difference in OS and PFS was reflected in stage 1 pts ($p < 0.02$ and <0.05; respectively) with a similar trend observed but not significant in non-stage 1 pts. Significant correlation was observed between gene and protein expression of tumour PD-1, tumour and stromal PD-L1, and tumour IL-6 using IHC ($p < 0.0001$ for all comparisons). 6 (8.1%) pts were MMR deficient with no significant association between ARID1A and MMR expression across each irGES.

Conclusions: OCCCs are heterogeneous and can be classified into 4 molecular subgroups based on their irGES profiles with distinct clinicopathological characteristics and prognostic outcomes. If validated in larger datasets, these signatures may serve to inform a clinical trial.

Legal entity responsible for the study: Institute Review Board SIngapore

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939PD An increased ratio of cytotoxic to suppressive T cells after neoadjuvant chemotherapy (NACT) is prognostic in advanced ovarian cancer

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Background: At diagnosis, tumor-infiltrating lymphocytes (TILs) are prognostic in epithelial ovarian cancer (EOC). We recently demonstrated that neoadjuvant chemotherapy (NACT) significantly increased stromal TILs and stromal TILs remained prognostically significant after NACT. Here, we investigated the impact of NACT on different immune subpopulations and their relationship with clinical outcome.

Methods: Tissue microarrays of EOC (145 pre-NACT, 139 post-NACT, including 83 matched samples) were analyzed for CD3+,CD8+ and FOXP3+ by immunohistochemistry. Stromal TILs scored as percentage of stromal area, intraepithelial TILs as number of TILs in contact with tumor cells/HPF. Differences were evaluated by Mann-Whitney or Wilcoxon-signed-rank for unpaired or paired analyses, respectively and by Log-rank for PFS and OS.

Results: NACT significantly increased stromal CD3 + ($p = 0.005$) and CD8 + ($p = 0.009$) and intraepithelial CD8 + ($p = 0.02$) infiltration in unmatched samples and remained significant among paired samples for stromal CD3+ and CD8 + ($p = 0.03$ and $p = 0.009$). Neither CD3+ nor CD8+ expression correlated with outcome at diagnosis or post-NACT, however reduced accumulation of FOXP3+ post-NACT (<5%) was significantly associated with improved PFS (HR = 0.59; $p = 0.016$). A high stromal CD8+/FOXP3+ ratio post-NACT strongly correlated with improved PFS (median 30.9 vs.18.85 mos, $p = 0.005$) and OS (median 50.70 vs 37.10mos, $p = 0.029$). In contrast, at diagnosis, CD8+/FOXP3+ was not associated with prognosis.

Conclusions: NACT has a significant impact on the balance of cytotoxic versus suppressive T cells and a high ratio of CD8+/FOXP3+ post-NACT was most significantly associated with improved PFS and OS. Whether this could select patients for immune therapies in the post-operative setting should be investigated.

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940PD Long term quality of life among epithelial ovarian cancer patients: The GINECO case/control VIVROVAIRE Study

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Background: If epithelial ovarian cancer (EOC) had a poor prognosis, more than 20% of patients (pts) can expected long remission. Few data are available on long term quality of life (QoL) in these pts and results reported were usually not compared to those of healthy controls. VIVROVAIRE was a large national case-control study comparing pts reported outcomes (PROs) among EOC pts without relapse within 3 years after first line treatment and a group of healthy women.

Methods: Pts were recruited in 27 French centers and clinical characteristics were issued from medical charts. Controls were randomized from electoral lists. Pts and controls matched on age. They filled in a form including PROs questionnaires: QoL, neurotoxicity and fatigue (FACT/G, FACT/O, FACT/GOG-Ntx, FACT/F), anxiety and depression (HADS), sleep disturbance (ISI) and Physical activity (IPAQ).

Results: 318 pairs were analysed (from 349 pts and 327 controls included). Median age: 65 (20-86), high level of education: 52% and 58%, respectively. Pts characteristics: FIGO stage I/II (49%), III/IV (47%) unknown (4%); major histology, serous (50%), endometrioid (16%), clear cells (8%), mucinous (4%). BRCA1/2 mutations (n = 21; 15%), unknown (n = 168). 99% of the pts had a surgery and 96% received platinum based chemotherapy, associated with antiangiogenic agent (14%) Interval from first line therapy: median 5 years [2 to 24]. Pts reported lower physical and functioning QoL scores ($p = 0.03$ and $p = 0.0002$), higher score of fatigue ($p < 0.0001$), and poorer quality of sleep ($p = 0.0003$) than controls. No difference of scores of anxiety and depression was observed between the 2 groups. TOI score (related to ovarian cancer and treatment) and score of neurotoxicity were higher among patients ($p < 0.0001$); 26% of pts reported severe fatigue, more than 70% of the pts were concerned about digestive symptoms and severe neurotoxicity. Only 18% of the pts and controls had an active physical activity.

Conclusions: Compared to healthy women, EOC pts presented poorer long term QoL, fatigue with important neurotoxicity and digestive symptoms. Physicians have to take in count of the late effects of treatments to help the pts to cope with the sequelae.

Legal entity responsible for the study: Centre François Baclesse

Funding: Fondation de France; Ligue Nationale Contre le Cancer

Disclosure: All authors have declared no conflicts of interest.

941PD An investigator initiated, open label, randomized, controlled, multicentric study, to assess the safety and efficacy of nimotuzumab (BIOMAb-EGFR) concurrent with cisplatin and radiotherapy (RT) in histologically documented squamous cell carcinoma of the cervix

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Background: EGFR inhibitors have proven to improve the efficacy of anticancer treatments in lung, colon, pancreas, or HNC. Results from studies show EGFR expression in cervical Ca to improve survival outcomes in the same. This study was designed to assess

safety and efficacy of Nimotuzumab with concurrent cisplatin and RT in patients with Ca Cervix.

Methods: In this open-label randomized controlled multicentric study 100 patients with histologically confirmed Ca Cervix were recruited over a 4 year period with an equal allocation of 1:1 for intervention (Standard arm- concurrent CTRT (Cisplatin 40mg/m2 weekly IV +RT) plus 200mg weekly BIOMAB IV (n = 50) on same day of cisplatin infusion) vs. standard arm only (n = 50). At 2 years data were available for 39 patients in the intervention arm and 35 patients in standard arm. The size of the lesion was documented using CT/PETCT at baseline. The response was analyzed using RECIST criteria at the following treatment every 3 months for subsequent 2 years. Toxicity was assessed using CTCAE v4 toxicity criteria.

Results: There were 74 evaluable patients at end of 2 years. The mean age was 49.6± 10.2 years. The complete response following treatment was seen in 37.8% (BIOMAB arm) of patients at two years following treatment compared to 38.2% in standard arm. However, progressive disease was seen more in standard arm (52.9%) compared to BIOMAB arm (35.1%). Best overall response was seen in 64.9% patients in the intervention arm compared to 47.1% patients in the standard arm at two years following treatment which is significant. At 2 years 60% progressed on standard arm compared to 37.5% in the intervention arm. The mean estimate of progression-free survival being 36 months vs. 56.5 months (BioMab arm) (Log rank Mantel-Cox $\chi 2 = 3.9$, $p = 0.05$). Except for one patient with Biomab sensitivity, there was no additional toxicity compared to the standard arm.

Conclusions: Nimotuzumab appears to be safe and effective targeted therapy in cervical cancer patients with long-term benefits.

Clinical trial identification: TS-01-2009

Legal entity responsible for the study: Healthcare Global Enterprises Ltd.

Funding: BIOCON

Disclosure: All authors have declared no conflicts of interest.

942PD Vanucizumab (VAN) in combination with atezolizumab (ATEZO) for platinum-resistant recurrent ovarian cancer (PROC): Results from a single arm extension phase of the phase I study BP28179

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Background: VAN is a bi-specific human IgG1 antibody, simultaneously blocking two key angiogenic factors, Ang-2 and VEGF-A. VAN as a single agent showed an objective response rate (ORR) of 29% in bevacizumab- naïve PROC. The anti-PD-L1 agent, ATEZO demonstrated a 22% ORR in advanced OC. Preclinical data suggested additive antitumor activity of VAN when combined with anti−PD-L1. Hence, treatment with VAN plus ATEZO has the potential to reverse pro-angiogenic and immune-suppressive signals, thereby resulting in improved clinical benefit.

Methods: Eligible patients (pts) had PROC measurable by RECIST 1.1. Pts with history of bowel obstruction, > 2 prior lines of systemic chemotherapy, or previous treatments with VEGF-A inhibitors or agents targeting Ang/Tie2 receptor axis were ineligible. Pts received VAN 2000 mg and ATEZO 840 mg, each IV Q2W, until disease progression or unacceptable toxicity. Primary efficacy endpoint was ORR as per RECIST 1.1, with tumor assessments every 8 weeks.

Results: 17 pts with median age of 63 years (range 45-74) were treated. Serous histology was present in all pts, except one clear cell subtype. 4 pts (24%) achieved confirmed PR, 8 pts (47%) experienced SD and 4 (24%) had PD, while one patient was not evaluable. The achieved RECIST ORR of 24% remained unchanged when evaluated as per immune-related response criteria. 9/17 pts were evaluable for CA-125 per GCIG criteria; three and two achieved a response with and without normalization respectively. The current estimate of PFS rate @ 6 months is 65% (median follow-up: 162 days). The most common adverse events (AE) of any grade (G) were decreased appetite, diarrhea (41% each), asthenia and constipation (35% each). AEs ≥ G3 included abdominal pain, LFT increase, asthenia, dyspnea, health deterioration, hypertension, GI obstruction, GI perforation (GIP), subileus, lymphedema, pleuritis and tonsillitis (6% each). One AE of GIP and asthenia each were fatal.

Conclusions: Our data suggest that VAN plus ATEZO does not improve upon monotherapy with VAN or ATEZO in PROC. The safety profile of this combination is consistent with reports for the single agents in this setting.

Clinical trial identification: NCT01688206

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

Funding: Roche

Disclosure: A. Oaknin: Advisory Board and/or Board of Directors for Roche, AstraZeneca, Clavis, PharmaMar. I. Vergote: Research (via KULeuven) for Amgen, Exelixis, Lilly, Morphotek, Pronota, Roche; Advisory Boards and/or Board of Directors for Roche, Genentech and multiple other pharmaceutical companies exceeding the character limit and thus not listed here. I. Ray-Coquard: Advisory Board for Roche. A. Leary: Advisory board and/or board of directors for AstraZeneca, Clovis, GamaMabs; Research funding: GamaMabs, Merus. A. Lahr, I. Franjkovic, S. Rossomanno, A. Sahbi, K. Longauer: Employment Roche. P. Gerber, F. Heil, C. Boetsch, O. Krieter: Stock options and employment Roche. T. Nayak: Stock options. All other authors have declared no conflicts of interest.

943P Location of mutation in BRCA2 gene and survival in patients with ovarian cancer

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Background: BRCA2 plays a central role in homologous recombination through loading RAD51 on DNA double strand breaks. Among ovarian cancer (OC) patients, carriers of *BRCA2* mutations have better survival than *BRCA1* carriers and non-carriers. The objective of this study is to determine whether location of mutations in *BRCA2* gene impacts survival of OC patients.

Methods: A study cohort of 340 women with OC, who underwent genetic germline testing for *BRCA1* and *BRCA2* genes and received platinum-based chemotherapy, were identified in four hospitals in Switzerland and France. Duration of follow-up was 4.14 years. The Cancer Genome Atlas (TCGA) cohort of high-grade serous ovarian carcinomas (n = 316) was used as a validation cohort. Progression-free survival (PFS) and overall survival (OS) were analyzed.

Results: In the study cohort, 74 and 78 patients were carriers of germline mutations of *BRCA1* and *BRCA2*, respectively. After adjustment for FIGO stage and macroscopic residual disease, *BRCA2* carriers having truncating mutations in the RAD51-binding domain (RAD51-BD; exon 11) have significantly prolonged 5-years PFS (58%; adjusted Hazard ratio [HR], 0.36; 95% CI, 0.20-.64; p=0.001) compared to non-carriers. *BRCA2* carriers with mutations located in other domains of the gene have not prolonged 5-years PFS (28%, adjusted HR, 0.67; 95% CI, 0.42-1.07; p=0.094). In the TCGA cohort, after adjustment for FIGO stage and macroscopic residual disease, only *BRCA2* carriers harboring germline or somatic mutations in the RAD51-BD had prolonged 5-years PFS (46%; adjusted HR, 0.30; 95% CI, 0.13-0.68; p=0.004) and 5-years OS (78%; adjusted HR, 0.09; 95% CI, 0.02-0.38; p=0.001), compared to non-carriers.

Conclusions: Among patients with ovarian cancer, *BRCA2* carriers having mutations located in RAD51-BD (exon 11) have prolonged progression-free survival and overall survival.

Legal entity responsible for the study: S. Intidhar Labidi-Galy

Funding: None

Disclosure: All authors have declared no conflicts of interest.

944P POLE mutations and MSI were positive predictive factors for progression free survival in endometrial cancer patients at the risk of recurrence

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Background: The Cancer Genome Atlas (TCGA) reported the genomic subgroups of endometrial cancer (EC); POLE mutation, Microsatellite instability (MSI), copy number low, and copy number high. Cancer with POLE mutation or MSI indicates hyper or high mutated, and they are considered to have some potential for good prognosis through immunoactivity in tumor microenvironment. In this study, we investigated the POLE mutation and MSI status in EC, and the correlation between the subtypes and prognosis and considered about the necessity of adjuvant therapy to good prognosis group.

Methods: In this study, we extracted tumor DNA from formalin-fixed, paraffin-embedded tissue of 325 EC tissues surgically resected at Okayama University

Hospital.Then, we analyzed MSI status from 4 mononucleotide markers by a multiplex PCR assay and *POLE* mutation status by Sanger sequence for hot spot mutations (V411L and P286R), and compared with the clinical and pathological outcomes obtained from medical records retrospectively.

Results: MSI cancer accounted for 24.9% (81/325 cases) and POLE mutation cancer accounted for 7.4% (24/325 cases) of the cohort. Progression free survival (PFS) was significantly better in POLE mutation group, followed by MSI group, and the others group. All the 24 POLE mutation patients had no recurrence during the observation period (median: 46.5 months [1∼111months]). Next, we investigated prognosis of the cases limited to those who usually need adjuvant therapy (except for stage IA and G1/2) among three genotype groups. POLE mutation and MSI group was the positive predictive factors for PFS in multivariate analysis.

Conclusions: POLE mutations and MSI were good prognostic factors for EC patients, especially, for EC patients at the risk of recurrence. Our results recommend prospective clinical trials whether adjuvant chemotherapy decreases the risk of recurrence in EC patients with POLE mutations or MSI.

Legal entity responsible for the study: Takeshi Nagasaka

Funding: None

Disclosure: All authors have declared no conflicts of interest.

945P Evaluation of circulating tumor DNA in patients with ovarian cancer harboring somatic PIK3CA or KRAS mutations

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Background: Circulating tumor DNA (ctDNA) is an important source for liquid biopsy to understand the molecular phenotype of a tumor non-invasively, and is also expected to be a diagnostic and prognostic marker in cancer patients. Our aim is to clarify the clinical features of ctDNA in patients with ovarian cancer.

Methods: We screened 304 patients with ovarian tumors for somatic PIK3CA or KRAS mutations by a PCR-based method. A total of 108 patients with ovarian tumors were found to have somatic PIK3CA and/or KRAS mutations. One hundred and four out of 108 patients were considered to be evaluable for ctDNA. Cell-free DNA from the plasma of patients before surgery was investigated using droplet digital PCR for PIK3CA or KRAS mutations. We defined ctDNA detection to be positive when the corresponding mutations were detected in the plasma cell-free DNA.

Results: In 104 patients, 75, 25, and 4 patients had malignant, borderline, and benign ovarian tumors, respectively. The detection rates for ctDNA were 32% (24/75), 16% (4/25), and 0% (0/4) in patients with malignant, borderline, and benign ovarian tumors, respectively. PIK3CA and KRAS mutations in the plasma cell-free DNA were detected in 33.3% (11/33) and 30.2% (13/43) of patients with malignant ovarian tumors, respectively. We investigated the relationship between ctDNA detection and clinicopathological features in 73 epithelial ovarian cancer (EOC) patients. The detection rate of ctDNA was associated with advanced stage ($p = 0.019$) and positive peritoneal cytology ($p = 0.011$), but not with the histologic subtype or residual tumor status. In addition, we examined the potential association of ctDNA with patient survival. In univariate analysis, ctDNA detection was associated with shorter progression-free survival in EOC patients ($p < 0.001$). Multivariate analysis revealed that the stage, residual tumors, and ctDNA were independently associated with an increased risk of recurrence.

Conclusions: ctDNA was detected in approximate 30% of EOC patients in this study regardless of histologic types or the genes examined. The presence of ctDNA in the blood was an independent prognostic factor for recurrence, which suggests potential tumor spread.

Legal entity responsible for the study: Department of Gynecologic Oncology, Saitama Medical University International Medical Center

Funding: Eisai Co., Ltd.

Disclosure: K. Hasegawa: Research grant from Eisai Co., Ltd. All other authors have declared no conflicts of interest.

946P Predictive and prognostic value of tumor cells and circulating plasma free DNA in advanced epithelial ovarian carcinoma

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Background: In recent years there has been increasing interest in the study of circulating tumor cells (CTC) and plama cell-free circulating DNA (cfDNA) as a new biomarker in neoplastic diseases. Our work aims to clarify its clinical role in ovarian epithelial carcinoma (OEC).

Methods: A prospective, multicenter, observational study has been conducted for 3 years in patients with advanced or responsive OEC. The predictive value and prognosis of CTC and cfDNA have been determined for both progression-free survival (PFS) and overall survival (OS). Their values have been compared with a control group. CTC were analysed by the CellSearch method and cfDNA by ALU-sequences-based quantitative PCR using two primers (ALU115 and ALU247); cfDNA integrity was calculated by ALU247/ALU115 ratio. This study was approved by the Central Research Ethics Committee. Updated data are presented.

Results: This study was conducted from November 2013 until December 2016. We recruited 88 patients, 15 benign tumors and 16 healthy subjects. Clinical characteristics were similar to other series, with a mean age of 57 years, 68.2% serous high grade subtype and 55.7% with stage IIIC. CTC were positive in 23.8% of patients (>1CTC/7,5mL). Levels of cfDNA were significantly elevated in patients than in the group of benign tumors and healthy control. CTC proved to be a negative prognostic factor of OS, with an average of 19.8 months versus 30.4 months (log-rank 4,649, $p < 0.031$). A high cfDNA value was also a negative prognostic factor for OS, with 22.5 months versus 28.7 months (log-rank 7.308, $p < 0.007$). The reduction in the integrity of cfDNA greater than 50% after chemotherapy was an early marker of resistance, with PFS of 6.4 months versus 16.0 months (HR 0.027, $p < 0.02$). The baseline value of cfDNA was also a negative prognostic factor for SLP, with 10 months versus 18 months (log-rank 7.233, $p < 0.007$). The baseline level of cfDNA and its integrity presented a predictive value of response to chemotherapy and the outcome of surgery, respectively.

Conclusions: In summary, CTC and cfDNA in advanced ovarian epithelial carcinoma have been prognostic factors for survival. In addition, cfDNA has a predictive value of response. These two biomarkers may be useful in clinical practice.

Legal entity responsible for the study: University Clinical Hospital Virgen Arrixaca - Murcia/ES

Funding: None

Disclosure: All authors have declared no conflicts of interest.

947P Circulating tumor cells as prognostic marker in ovarian carcinoma: Results from the ANTHALYA study

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Background: Circulating tumor cells (CTC) are detected in 12–30% of advanced stage/relapsing ovarian carcinoma (OC). We evaluated the prognostic value of CTC counts among patients (pts) from the ANTHALYA trial, an open-label randomized phase II study evaluating addition of bevacizumab (Beva) to neoadjuvant carboplatin-paclitaxel (CP) in first line for pts with unresectable FIGO stage IIIc/IV ovarian, tubal or peritoneal adenocarcinoma.

Methods: We obtained CTC counts at baseline and before interval debulking surgery (IDS). A CTC threshold of ≥ 1 CTC/7.5 mL blood was considered as CTC+. We assessed the prognostic impact of CTCs on objective response rate (ORR), interval

Table: 947P

Prognostic approach	**0 CTC at baseline (n = 59)**		**CTC+ at baseline (n = 29)**	
ORR at IDS	59.3%		75.9%	
Median PFS [95% CI]	25.8 m [18.5-27.2]		21.0 m [15.0-25.4]	
Predictive approach	**Beva (n = 36)**	**CP (n = 23)**	**Beva (n = 17)**	**CP (n = 12)**
ORR at IDS	61.1%	56.5%	82.4%	66.7%
Median PFS [95% CI]	25.8 [20.9-NE]	20.3 [13.8-27.2]	21.0 [15.0-30.6]	20.6 [8.0-25.4]
Progression rate at M36	36.1%	56.5%	52.9%	83.3%

debulking surgery (IDS) rate, complete resection rate and progression-free survival (PFS), and explored their potential predictive impact on ORR and PFS according to bevacizumab therapy.

Results: In 88 pts with an available CTC count at baseline, CTC+ pts (n = 29) had a 75.9% ORR (at IDS), vs 59.3% for pts with 0 CTC (n = 59): OR = 2.2 [0.8-5.8] (OR-adj=1.8 [0.8-5.8]). Respectively, 58.6% vs 66.1% were amenable to IDS and 55.2% vs 54.2% achieved a complete resection. Median PFS was 21 m [15.0-25.4] in CTC+ pts and 25.8 m [18.5-27.2] in pts with 0 CTC (HR = 1.5 [0.8-2.8] and HR-adj=1.7 [0.9-3.2]). CTC counts at IDS were available in 70 pts. At IDS, a complete resection was achieved in 66.7% of CTC+ pts (n = 6), and in 68.8% of pts with 0 CTC (n = 64). Exploration of the potential predictive impact of CTC is described in the table.

Conclusions: Baseline CTC counts in OC patients receiving neoadjuvant chemotherapy +/- bevacizumab carry dual prognostic information: CTC count at IDS do not add any information, CTC+ seems to be associated with a higher ORR, while 0 CTC count seems to be a prognostic factor with better PFS, in the whole population and among patients treated with bevacizumab.

Clinical trial identification: 2012-01144-22

Legal entity responsible for the study: ROCHE

Funding: Roche

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981P Reactive stroma mediates CD8+ T cell spatial distribution and function in ovarian cancer

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Background: Close proximity between cytotoxic T cells and tumor cells is key to effective immunotherapy. Ovarian cancer exhibits diverse immune phenotypes with distinct prevalence and spatial localization of CD8+ T cells. This study is aimed to characterize the molecular mechanisms orchestrating the localization and function of CD8+ T Cells in ovarian cancer.

Methods: CD8 IHC and RNAseq were performed on 277 ovarian tumor tissues from ICON7 phase 3 trial. CD8 T-cells in tumor vs. stromal area was assessed by digital pathology. A Random Forest regression model was constructed to identify molecular features associated with enumeration or spatial localization of CD8+ T cells. *In situ* validation was performed by MHCI IHC and FAP RNAish. Functional role of ovarian fibroblasts was characterized by *ex vivo* T cell function assays.

Results: We identified three main immune phenotypes, including T-cell infiltrated, T-cell excluded, and immune desert. The immune phenotypes are highly associated with prognosis and the molecular subtypes of ovarian cancer. The T-cell infiltrated phenotype is denoted by high expression of T-effector signatures and antigen presentation machinery. The T-cell excluded phenotype showed similar expression of T-effector signatures as the T-cell infiltrated phenotype, however, most of the CD8+ T-cells were excluded from the tumor bed. The T-cell excluded phenotype showed high expression of the reactive stroma signatures (i.e. FAP), and low expression of class I antigen presentation genes. Lastly, the immune desert phenotype featured low prevalence of CD8+ T-cells, and high expression of neuroendocrine and metabolic pathways. In situ analysis confirmed the two key molecular features associated with the T-cell excluded phenotype: 1) loss of the MHC I expression in the tumor compartment, and 2) high FAP expression in CAFs. Co-culturing of ovarian fibroblast cells with T-cells resulted in reduced T-cell activation and proliferation.

Conclusions: Our study uncovered key molecular mechanisms mediating the interplay between CD8+ T cell localization and function in ovarian cancer. Our findings underscore the potential of targeting reactive stroma as a novel therapeutic strategy to optimize immunotherapy for ovarian cancer patients.

Legal entity responsible for the study: Genentech

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Disclosure: Y. Wang, L. Ryner, A.R. Udyavar, M. Desbois, C. Kozlowski, C-W. Chang, Y. Guan, S. Lu, H. Koeppen, J. Ziai, R. Bourgon, P.S. Hegde: Employee and Stock holder of Genentech/Roche.

948P Genomic instability is associated with increased immune infiltration and PDL1 expression in epithelial ovarian cancer

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Background: High mutation load secondary to mutagenic exposures such as smoking or to mutations in mismatch DNA repair genes has been associated with increased tumor immune infiltration and response to immune therapies. Ovarian cancers (OC) demonstrate low mutation load, but high degree of genomic instability (GI) attributable to frequent defects in the homologous recombination DNA repair pathway. We sought to investigate whether GI predicted increased infiltration by tumor infiltrating lymphocytes (TILs) and PDL1 expression in OC.

Methods: TILs were evaluated on FFPE OC samples and scored as percentage of stromal area. PDL1 expression was quantified as percent positive immune cells. GI was measured as the number of copy number alterations >15Mb by Oncoscan SNParray on DNA from the same FFPE samples and high GI score (GIS) defined as > median. Correlations were evaluated using a Spearman rank and differences by Mann-Whitney.

Results: 66 tumor samples were evaluable for both GIS and immune infiltration. GIS and TILs showed significant variability ranging from 0 to 64 (median=28) and from 5 to 90% (median=20%) for GIS and TILs, respectively. GIS was significantly higher among high grade serous or endometrioid OC than among low grade tumors (GIS=29 vs 5; $p < 0.0001$) and non-significantly greater among patients with *BRCA* mutations and/or family history compared to wild-type OC with no family history ($p = 0.12$). GIS and TILs were highly correlated ($R = 0.4$; $p = 0.0019$) and median TILs were significantly increased in GIS-high vs -low tumors (29% vs 15%; $p = 0.0028$, Fig 1) as was immune cell PDL1 expression ($p = 0.025$). Fig 1 Increased TILs in tumors with high genomic instability

Conclusions: High genomic instability correlated with increased tumor infiltrating lymphocytes and PDL1 expression. Whether GIS could provide a simple and predictive biomarker for immune therapies in OC should be investigated.

Legal entity responsible for the study: LEARY Alexandra

Funding: INCa (Institut national du cancer)

Disclosure: All authors have declared no conflicts of interest.

949P Tumor microenvironment in high serous ovary cancer: Characterization of the infiltration pattern and analysis of its prognostic value

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Background: Lymphocytic infiltration areas (immunoreactive) are frequently found in ovarian cancer, which is associated with a better prognosis and increased survival. Therefore, the study of different patterns and degree of infiltration would help us to better understand the relationship between immune and tumor cells and its prognostic implications.

Methods: This retrospective study includes samples from 57 patients with high grade serous ovarian cancer (HGSOC) who underwent cytoreductive surgery. The pattern of infiltration, localization and degree of lymphocyte infiltration in the tumor was evaluated. A set of clinical variables such as smoking, age, type of surgery, intention of treatment, type of response, as well as lymphocytic infiltration were evaluated to assess prognosis.

Results: In our cohort, the median age was 61.5 years, there were 60% of smokers, and most of the cases were FIGO stages III and IV (15.3%, stage I, 8.5% stage II, 54.3% stage III and 22% stage IV). As expected, patients over 65 years, as well as the group of more advanced stages (III and IV) showed a shorter overall survival (OS, 30.17 vs 99.90 months, $p = 0.009$; 38.73 months vs NR, $p = 0.005$, respectively). Smoking status was also analyzed but no significant effect on survival was found (OS, $p = 0.935$). Interestingly, patients with an intratumoral lymphocyte infiltrate had better prognosis compared to the group that had only a peritumoral pattern (OS, 44.57 months vs NR, $p = 0.041$). In addition, those with a diffuse infiltration pattern presented a better prognosis compared to those with a focal pattern (OS, 20.20 months vs NR $p = 0.003$). Finally, a tendency for a better OS was seen for those patients with a strong degree of infiltration in the tumor.

Conclusions: HGSOC represents a group of highly immunoreactive tumors. Those with the best prognosis are represented by an intratumoral, diffuse pattern with a strong degree of infiltration, these findings could open a new window for therapeutic approaches in HGSOC.

Legal entity responsible for the study: Fundación de Investigación Hospital General de Valenecia

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950P Gene mutational analyses in 154 ovarian cancer (OC) samples from the ROSiA study of front-line bevacizumab (BEV)-containing therapy for OC

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Background: In the single-arm ROSiA study (NCT01239732), 1021 patients (pts) with newly diagnosed OC received 12–24 wks of carboplatin + paclitaxel with BEV for up to 24 mo or until progression [Oza 2016]. Progression-free survival (PFS) was a secondary endpoint.

Methods: In an optional translational research substudy, tumour tissue samples collected before BEV were analysed using Foundation Medicine Inc.'s FoundationOne® (FMOne) gene panel. Prevalence of gene alterations, tumour mutational burden (TMB) and potential prognostic effects were assessed in exploratory gene mutational analyses using Cox proportional hazards models. Correlations between TMB and *BRCA1* mutation and immunohistochemical expression of the immune markers PD-L1 and CD8 were assessed.

Results: The FMOne population ($n = 154$) was representative of the ITT population ($n = 1021$) for baseline characteristics but had slightly more favourable PFS (median 30.2 vs 25.5 mo, respectively; hazard ratio [HR] 1.16 [95% CI 0.92–1.45]; $p = 0.21$). The most common gene alterations (predominantly short variant) were *TP53* (79% of pts), *BRCA1* (22%), *NF1* (14%), *KRAS* (10%), *PIK3CA* (9%) and *BRCA2* (7%). *MYC*, *TERC*, *GNAS* and *CCNE1* were amplified in 25%, 16%, 7% and 7%, respectively. The mean TMB (excluding germline polymorphisms and known cancer drivers) was 4.5/megabase (Mb; range 0–43). Only 2 pts had a TMB >15/Mb; 43 had a TMB ≥5/Mb. In univariate Cox regression analyses, none of the mutations explored showed a clear association with PFS. PFS slightly (not statistically significantly) favoured pts with ($n = 34$) vs without ($n = 118$) *BRCA1* mutation (median 30.4 vs 28.1 mo, respectively; HR 0.76 [95% CI 0.44–1.31]; $p = 0.32$). TMB and PFS showed no association. No meaningful correlations were seen between either TMB or *BRCA1* mutation and expression of the immune markers PD-L1 and CD8 on immune cells.

Conclusions: Samples from pts with newly diagnosed OC indicated relatively infrequent gene alterations and low TMB. None of the gene alterations evaluated suggested prognostic value, but low frequency of these mutations and the relatively small number of samples in ROSiA limit interpretation, particularly for the correlation analyses.

Clinical trial identification: NCT01239732

Legal entity responsible for the study: F Hoffmann-La Roche Ltd

Funding: F Hoffmann-La Roche Ltd

Disclosure: R. Deurloo, Y. Ghazi: Employee, shares: F Hoffmann-La Roche. N. Colombo: Travel expenses from Roche for ROSiA steering committee meetings, personal fees from AstraZeneca and PharmaMar for advisory boards and speaker engagements, and personal fees from Clovis, Amgen, MSD, and Pfizer for advisory boards. C. Mendiola: Non-financial support from Roche Farma Spain and AstraZeneca Spain. F. Selle: Honoraria for consultant/advisory role: Roche; travel/accommodation expenses: Roche, AstraZeneca. M.Z. Oestergaard, H-J. Urban: Employee: F Hoffmann-La Roche. M. Bylesjo: Employee of Fios Genomics Ltd, a contract research organisation contracted to provide statistical services to F Hoffmann-La Roche Ltd. A. Oza: Travel expenses from Roche for advisory boards and ROSiA steering committee meetings. All other authors have declared no conflicts of interest.

951P A retrospective study of endocrine therapy in high grade serous ovarian carcinoma

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Background: The degree of oestrogen receptor (ER) expression in ovarian cancer correlates well with its endocrine sensitivity. However, the use of endocrine therapy (ET) in relapsed disease is variable in part due to the lack of phase III data. It is thus unlicensed and not a standard of care. Here we describe the endocrine sensitivity of high grade serous ovarian carcinoma (HGSOC) in a large retrospective cohort.

Methods: Patients were eligible if they had HGSOC treated with prior chemotherapy, and received at least 4 weeks of ET. Exclusion criteria included: ET as a maintenance treatment and unknown duration of therapy (DOT). The best CA125 response across the DOT was recorded as per modified GCIG criteria. Stable CA125 response had to be maintained for at least 12 weeks. The primary endpoint was DOT. Secondary endpoints

Table: 951P

ER histo-score	CA125 CBR (%)		DOT (days)		Median TTNT (days)	
≥150 vs < 150	51.5 vs 45.5	n/s	HR = 0.62 [95% CI 0.43-0.89]	Median: 133 vs 93 p = 0.039	164.5 vs 118	p = 0.075
≥200 vs < 200	57.3 vs 37.5	p = 0.029	HR 0.69 [95% CI 0.52-0.91]	Median 141.5 vs 92 p = 0.001	171 vs 118	p = 0.008

were time to next therapy (TTNT) from treatment initiation, CA125 objective response rate (ORR) and clinical benefit rate (CBR).

Results: 593 patients were identified from the Edinburgh Ovarian Cancer Database between January 1974 and December 2015. 267 patients met the eligibility criteria (78.3% letrozole, 19.5% tamoxifen, 2.2% megestrol acetate). Median DOT and TTNT were 122.5 days (range 28-1427 days) and 161 days (range 41-2345 days), respectively. 33.2% and 14.6% of patients received ET for ≥ 180 and ≥ 365 days, respectively. Of 38 patients on ET for ≥ 365 days, 29 (76%) received ET as 2nd line therapy, 9 (24%) as 3rd line therapy and none as 4th line or later. The CA125 ORR and CBR in evaluable pts was 11.4% (20/175) and 48.6% (85/175), respectively. The CA125 CBR, median DOT and TTNT between different ER histoscore ranges are compared in *Table.* In early (2nd line) vs late (3rd line onwards) use of ET, the median DOT and TTNT was 140 vs 98 days (HR = 0.68 [95% CI 0.53-0.87]) and 167 vs 138 days (p = 0.022), respectively.

Conclusions: The endocrine sensitivity of HGSOC is significantly influenced by the degree of ER expression and line of treatment that ET is used in. Early introduction of ET in the management of relapsed HGSOC should be considered particularly in tumours with an ER histoscore of ≥ 200.

Legal entity responsible for the study: Professor Charlie Gourley

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952P Randomised prospective study of maintenance tamoxifen versus post adjuvant chemotherapy surveillance only in advanced ovarian cancer patients

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Background: Treatment of advanced ovarian cancer results in a high objective response rate (> 70% to 80%), but disease recurs in most patients. Some studies have been done to understand the role of maintenance therapy after conventional adjuvant chemotherapy. Maintenance therapy must balance prevention of disease recurrence with cumulative toxic effects and reduction in quality of life. The effects of maintenance therapy with chemotherapy (e.g. paclitaxel maintenance) or antiangiogenetic agents (e.g. bevacizumab or pazopanib) have been studied, but results have been conflicting and without significant benefit in overall survival. We have performed this study to assess the role of maintenance tamoxifen post adjuvant chemotherapy in patients with advanced ovarian cancer.

Methods: In this prospective study, done in a tertiary care centre in northern India, patients with advanced ovarian cancer (stage III and IV), post conventional adjuvant chemotherapy, were randomly enrolled from Sep 2012 to April 2015. Tamoxifen maintenance was given at a dose of 20 mg twice a day for entire follow up period. The progression free survival (PFS) was analyzed.

Results: In total 100 patients were enrolled: 50 patients were given tamoxifen and 50 patients were put on post adjuvant treatment surveillance. The median age was 51.0 years (31-69 years). Median follow up of these patients was 14 months (6-22 months). Median increase in PFS was 6.3 months (95% CI: 4.52-6.14 months) in patients treated with maintenance tamoxifen and there were no grade 3/4 side effects seen in this group.

Conclusions: Maintenance tamoxifen prolongs PFS by 6.3 months when compared to no treatment after conventional adjuvant chemotherapy. Further studies should be planned for comparison of maintenance tamoxifen with maintenance chemotherapy (e.g. paclitaxel maintenance) or antiangiogenetic agents.

Legal entity responsible for the study: Rajiv Gandhi Cancer Institute and Research Center

Funding: None

Disclosure: All authors have declared no conflicts of interest.

953P A phase 1 study to evaluate the safety and tolerability of bevacizumab-niraparib combination therapy and determine the recommended phase 2 dose (RP2D) in women with platinum-sensitive epithelial ovarian cancer (ENGOT-OV24/AVANOVA1)

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Background: A phase 2 randomized study has indicated that the combination of a poly(ADP-ribose) polymerase inhibitor (PARPi) with an anti-angiogenic drug is superior to PARPi alone.

Methods: Bevacizumab 15 mg/kg IV q 21 days (fixed dose) was administered with escalating dose of niraparib capsules (100, 200, 300 mg daily) in a classic 3 + 3 escalation design. Platinum-sensitive ovarian cancer patients (pts) with high-grade serous/endometrioid carcinoma and with measurable disease (RECIST or GCIG criteria) were eligible. The primary objective was to evaluate the safety and tolerability of the bevacizumab-niraparib combination therapy and determine the RP2D of bevacizumab-niraparib.

Results: Twelve pts (3 + 3+6) were enrolled to three dose levels. Three of 12 pts had g*BRCA*2 mutation, while the others were non-g*BRCA*mut. During the first cycle, patients experienced hypertension (G3=5 pts), anemia (G3=3 pts), thrombocytopenia (G3=1 pt), fatigue (G2=1 pt), constipation (G2=1 pt), and nausea (G2=1 pt). One dose-limiting toxicity (Grade 3 thrombocytopenia that persisted for ≥5 days) was observed at the highest dose level, and the RP2D is therefore bevacizumab 15 mg/kg with niraparib capsules 300 mg. Niraparib dose reductions occurred in four pts (cohort 2=1 pt; cohort 3=3 pts), and bevacizumab termination occurred in two pts. Three pts are still on treatment, while nine pts have discontinued treatment (8 progressive disease; 1 withdrawal of consent). Disease control rate was 91%, and response rate was 45% (1 CR; 4 PR). Niraparib pharmacokinetics were consistent with historical data. Overlapping exposure was observed across the dose range tested at both C1D1 and C2D1.

Conclusions: The bevacizumab-niraparib combination has hematologic dose-limiting toxicity and expected, manageable class toxicities with preliminary evidence of efficacy. The PK profiles of niraparib co-administered with bevacizumab are similar to historical data. A phase 2 randomized 2-arm trial is ongoing (AVANOVA2, NCT02354131).

Clinical trial identification: NCT02354131

Legal entity responsible for the study: Nordic Society for Gynaecologic Oncology

Funding: TESARO, Inc.

Disclosure: M.R. Mirza: Advisory board: Tesaro, Roche, AstraZeneca & Clovis Oncology. J. Wang, X. Wang, Z-Y. Zhang, V. Kansra: Employment: Tesaro; Stock: Tesaro. M. Mau-Sørensen: Research grants and support to participate in conferences from Roche. S. Malander: Honoraria: AstraZeneca, Roche. All other authors have declared no conflicts of interest.

954P Prospective cohort study of bevacizumab plus standard platinum based chemotherapy as front-line treatment for advanced epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer: Japanese Gynecologic Oncology Group study (JGOG3022)

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Background: The GOG-218 and ICON-7 studies showed that addition of bevacizumab (BEV) to front-line treatment for patients (pts) with advanced ovarian cancer increased progression free survival. Based on this result, BEV has been widely used in the front-line treatment. However, sufficient safety information of addition of BEV is not available in Japan. This prospective cohort study is conducted to assess the safety of addition of BEV to front-line treatment.

Methods: Eligible pts have FIGO stage III–IV epithelial ovarian, fallopian tube or primary peritoneal carcinoma, were aged ≥20 years and have ECOG PS 0–2. Prior neoadjuvant chemotherapy was permitted. The primary cohort was defined as pts who received tri-weekly paclitaxel/carboplatin (PC) plus BEV, and the exploratory cohort as pts who received other platinum based regimen plus BEV. BEV is continued at the same dose as a single agent until disease progression or unacceptable toxicity. The primary objective is to assess safety (NCI-CTCAE v4.03) of the primary cohort.

Results: A total of 346 pts (Primary/exploratory cohort: 303/43) were enrolled from 79 institutions from Apr 2015 to Feb 2016. The data of primary cohort of 293 pts were analyzed as of 31 Mar 2017. The median age was 58 years (range: 27–83). The majority of the histologic type was Serous adenocarcinoma (65.2%) followed by Clear cell adenocarcinoma (12.3%) and Endometrioid adenocarcinoma (10.6%). Up-front surgery was performed in 203 pts (69.3%), and interval debulking surgery following neoadjuvant chemotherapy was performed in 90 pts (30.7%). A total of 45 serious adverse events occurred. Two pts (0.6%) developed a gastrointestinal perforation (grade 2) or fistula (grade 3). Thromboembolic events, hypertension, and hematuria of grade 3 or greater occurred in 3 (1.0%), 2 (0.7%), and 1 pt (0.3%), respectively.

Conclusions: Addition of bevacizumab to platinum based front-line chemotherapy can be safely administrated for advanced ovarian cancer pts in Japan. The rates of gastrointestinal and thromboembolic toxicity were relatively low as compared with the previous studies.

Clinical trial identification: JGOG3022

Legal entity responsible for the study: Japanese Gynecologic Oncology Group

Funding: Chugai Pharmaceutical Co., Ltd.

Disclosure: All authors have declared no conflicts of interest.

955P A landmark analysis of overall survival in PR-OC patients treated with chemotherapy and bevacizumab using early tumor shrinkage as covariate

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Background: We aimed at developing a OS model incorporating TK metrics in platinum-resistant (PR)-ovarian cancer (OC) patients using data from the randomized, open label, phase 3 AURELIA trial designed to compare PFS in patients treated with chemotherapy alone (CT) or in combination with Bevacizumab (B).

Methods: Individual data from 361 patients randomly allocated to the B+CT or CT were available. Three types of CT were evenly distributed in both arms. Tumor size reported as sum of lesion diameter (SLD, RECIST 1.0) was collected at baseline and every 8 to 9 weeks until disease progression. Patients continued to be followed for OS even after treatment discontinuation. A non-linear mixed effect TK model accounting for the dynamics of tumor growth, drug effect and treatment resistance was used to fit the SLD. The final TK model contained a term of resistance specific to each CT type in both study arms while drug effect and tumor growth rate were common to all patients. TK metrics indicated that most of the patients experienced tumor shrinkage with a more profound shrinkage in the B+CT arm. From this model, two TK metrics were derived for each patient: early shrinkage at week 8 (ETS8) and predicted SLD at treatment onset (TS0). Then a Cox proportional-hazard survival model was developed. Covariates including ECOG and FIGO score at baseline, histological grade and subtype, time from 1st diagnosis to treatment onset, presence of ascites, CA-125 at baseline, TS0, and ETS8 were tested as prognostic factors.

Results: In the bootstrap-based covariate analysis, two sets of factors were found to be influential on survival time: those reflecting the disease severity (ECOG, FIGO stage, presence of ascites) and those describing key features of the TK (ETS8 and TS0). Treatment group was not retained in the final model as its effect was masked by the influence of the other covariates.

Conclusions: For the 1st time, an OS model including individual TK metrics was developed for PR-OC patients. This analysis confirms previous findings indicating the low predictive value of CA-125 in this population. While treatment group and baseline CA-125 were not found to influence survival time, model derived TK metrics were predictive of OS, ETS8 notably.

Clinical trial identification: AURELIA study: NCT00976911 Completed July 2014

Legal entity responsible for the study: F. Hoffman La Roche Ltd

Funding: F. Hoffman La Roche Ltd

Disclosure: A. Sostelly: Employee of F-Hoffman La Roche (Basel, Switzerland). F. Jaminion, F.J. Mercier: Employee of F. Hoffman-La Roche Ltd.

956P Influence of comorbidities on clinical outcome in patients (pts) receiving chemotherapy (CT) + bevacizumab (BEV) for primary advanced ovarian cancer (OC)

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Background: Using interim data from the single-arm non-interventional OTILIA study (NCT01697488; NOGGO) of front-line BEV + CT for OC in routine practice, we explored the impact of pre-existing comorbidities on clinical outcome.

Methods: Pts with FIGO stage IIIB–IV OC received front-line BEV + CT according to the EU label. Adverse events (AEs; CTCAE v4.0) were recorded at each cycle. Post hoc analyses explored safety and effectiveness in subgroups of pts with diabetes mellitus, ongoing hypertension (HTN) or cardiovascular (CV) comorbidities (coronary heart disease, heart failure, arrhythmia, ongoing HTN, thromboembolic event).

Results: As of 31 Jan 2017, data were available for 808 of 1190 planned pts. Comorbidities were more common in pts aged ≥70 (n = 382) than <70 y (n = 426). Baseline characteristics and outcomes in the three subgroups are shown below. Logistic regression models suggested a higher risk of non-haematological AEs in pts with CV comorbidities (odds ratio [OR] adjusted for key prognostic factors: 1.75; $p = 0.009$) or HTN (OR 1.89; $p = 0.046$), and of CV events in pts with CV comorbidities (OR 3.12; $p < 0.001$). There was no relevant difference in progression-free survival (PFS) between subgroups. Further subgroup analyses of PFS according to HTN (pre-existing vs treatment emergent vs none) suggested the longest PFS in 132 pts developing HTN during therapy (median PFS 26.5 mo). However, a Cox regression analysis to account for the confounding effect of BEV duration indicated that HTN development was not a significant predictive factor for PFS.

Conclusions: In OTILIA, pts with comorbidities had similar PFS to the overall population, despite older age and worse ECOG PS. Grade 3/4 AEs were slightly more common, particularly in pts with diabetes mellitus, but did not lead to treatment discontinuation. These post hoc analyses suggest that with appropriate care, BEV is an option in pts with comorbidities.

Clinical trial identification: NCT01697488

Legal entity responsible for the study: Roche Pharma AG

Funding: Roche Pharma AG

Disclosure: H. Woopen: Membership on advisory board or board of directors: Roche Pharma AG. P. Wimberger: Membership on advisory board or board of directors: Roche, Novartis, Amgen, AstraZeneca, MSD, TEVA, Pharma Mar, Fresenius Biotech; Corporate-sponsored research: Roche, Novartis, Amgen, Fresenius Biotech, MSD. A. Mustea: Membership on advisory board or board of directors: Roche. S. Klawitter, A. Wegenaer: Employment: Roche Pharma AG. J. Sehouli: Membership on advisory board or board of directors: AstraZeneca, Roche, OBI Pharma, Pfizer, Clovis, NovoCure. All other authors have declared no conflicts of interest.

Table: 956P

Baseline characteristic, n (%)		All pts (n = 808)	Pts with CV comorbidities (n = 445)	Pts with pre-existing HTN (n = 406)	Pts with diabetes mellitus (n = 83)
Median age, y (range)		68 (26–83)	71 (33–83)	72 (33–83)	72 (46–83)
Age ≥70 y		382 (47)	262 (59)	252 (62)	52 (63)
ECOG PS[a]	0	297 (37)	144 (32)	133 (33)	24 (29)
	1	378 (47)	219 (49)	199 (49)	38 (46)
	2	72 (9)	44 (10)	39 (10)	11 (13)
Ongoing CV comorbidities		445 (55)	445 (100)	406 (100)	67 (81)
	Pre-existing HTN	406 (50)	406 (91)	406 (100)	64 (77)
Diabetes mellitus		83 (10)	67 (15)	64 (16)	83 (100)
No macroscopic residuum		220 (27)	120 (27)	107 (26)	18 (22)
Ascites >500 mL		99 (12)	63 (14)	57 (14)	9 (11)
Grade 3/4 AEs		301 (37)	189 (42)	177 (44)	42 (51)
Treatment discontinued		433 (54)	233 (52)	209 (51)	50 (60)
Reason for treatment discontinuation	Disease progression	134 (17)	72 (16)	69 (17)	12 (14)
	15 mo' documentation completed	82 (10)	43 (10)	33 (8)	7 (8)
	Treatment-related AE[b]	67 (8)	38 (9)	37 (9)	5 (6)
	Patient request	47 (6)	20 (4)	17 (4)	8 (10)
	Death	19 (2)	15 (3)	12 (3)	3 (4)
Median BEV duration, mo (range)		13.4 (12.8–13.8)	13.4 (12.5–13.8)	13.5 (12.5–13.8)	11.3 (8.1–13.6)
Median PFS, mo (95% CI)		21.3 (20.3–22.5)	21.3 (20.1–23.1)	21.3 (20.0–23.1)	20.2 (16.8–26.2)

[a]ECOG PS 3 in 14 pts, missing/unknown in 47 pts.

[b]Reported as 'side effects of therapy' until Aug 2013. ECOG PS=Eastern Cooperative Oncology Group performance status.

957P Feasibility and effectiveness of multiple lines of bevacizumab-based therapy in patients with recurrent tuboovarian carcinoma

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Background: In metastatic breast cancer, bevacizumab (Bev)-based treatment beyond progression (TBP) has been found a valid option, whereas TBP with Bev in tuboovarian carcinoma (TOC) has not been intensively investigated so far. This retrospective study sought to investigate the feasibility and effectiveness of multiple lines of Bev-based systemic therapy (Tx) in patients (pts) with recurrent TOC.

Methods: From our database, a total of 90 pts with recurrent TOC (45 with platinum-sensitive or platinum-resistant disease each) receiving at least one line of Bev-based Tx were identified. 37 (41.1%) pts had one, 20 (22.2%) two, 13 (14.4%) three, and 20 had (22.2%) 4-9 lines of Bev. A total of 225 courses of Bev-based Tx were administered: 58 (25.8%) as monotherapy (Bev), 63 (28.0%) in combination with conventionally dosed chemotherapy (Bev+cCtx), and 104 (46.2%) in combination with metronomic Ctx (Bev+mCtx). Time to progression (TTP) was calculated from the start of each Bev-based Tx until progression, overall survival was calculated from the start of the first Bev-based Tx until death from any reason or loss to follow-up. Adverse effects in regard to Bev were scored according to CTCAE vs 4.02.

Results: Most frequent side effects of Bev were proteinuria occurring in 50%, hypertension in 41%, gastrointestinal toxicity in 31%, and infection in 17% of treatments. However, G3-4 toxicities were rare with hypertensive crisis in 2.2%, bowel obstruction in 0.9%, bowel perforation in 0.9%, nephrotic syndrome in 0.4% and infection seen in 1.3% of treatments. Both TTP and OS did not differ between different types of Tx. TTP: Bev, 5.4 months (mts); Btsv+cCtx, 6.1 mts; Bev+mCtx, 6.3 mts. OS: Bev, 28.6 mts, Bev+cCtx, 31 mts; B+mCtx, 21.4 mts. TTP for platinum-resistant vs platinum-sensitive pts was 4.5 and 7.6 mts (p=NS) and OS was 20.1 vs 12.2 mts ($p = 0.044$). TTP was comparable between one and multiple lines of Bev: one line, 6.6 mts; two lines, 6.3 mts, three lines 5.9 mts, and 4-9 lines 3.7 mts ($p = 0.130$). However, OS increased significantly with the number of Bev-based lines of Tx: one line, 8.8 mts; two lines, 16.8 mts; three lines 25.4 mts; 4-9 lines, 36.6 mts ($p = 0.0001$).

Conclusions: Our results demonstrate that retreatment with Bev can be safely given to pts with recurrent TOC in the clinical routine. The incidence of severe side effects was generally low and did not increase by the line of Bev-based Tx. However, the number of Bev-based lines had a significant impact on overall survival. Thus, rechallenge with Bev may be a valuable option in the treatment of recurrent TOC.

Legal entity responsible for the study: Christian M. Kurbacher

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Disclosure: C.M. Kurbacher: Author received honoraria from Roche, Amgen, Novartis, Teva Oncology, Riemser. All other authors have declared no conflicts of interest.

958P Impact of body mass index (BMI) on outcome in 785 patients (pts) receiving systemic chemotherapy (CT) and bevacizumab (BEV) for primary advanced ovarian cancer (OC) (on behalf of the North-Eastern German Society of Gynaecological Oncology, NOGGO)

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Background: The GOG-0218 and ICON7 randomised phase III trials demonstrated the efficacy and safety of front-line BEV + CT for OC. The single-arm OTILIA study is evaluating BEV + CT in German clinical practice. In a previously reported interim analysis (ESMO & IGCS 2016), the observed safety and effectiveness were consistent with phase III results (preliminary median progression-free survival [PFS] 21.7 months). To address the lack of data on the impact of BMI on safety and clinical outcome in pts receiving CT + BEV, we performed exploratory analyses of the OTILIA dataset.

Methods: In OTILIA (NCT01697488), pts with FIGO stage IIIB–IV OC received front-line BEV + CT according to the EU label. Adverse events (CTCAE v4.0) were recorded at each cycle. Investigators assessed response per local practice. We performed post hoc exploratory subgroup analyses of the third interim dataset according to BMI and a multiple Cox regression analysis of PFS vs BMI, age, ECOG performance status, FIGO stage, residual disease and ascites as covariates.

Results: BMI was available for 785 of 808 pts. Treatment duration was similar across BMI subgroups (Table). There were no significant differences in PFS between

Table: 958P

Parameter, n (%)		BMI, kg/m^2			
		≤20 (n = 107)	>20–25 (n = 329)	>25–≤30 (n = 237)	≥30 (n = 112)
Age ≥70 years		35 (33)	162 (49)	117 (49)	51 (46)
ECOG performance status ≥2		13 (12)	31 (9)	24 (10)	16 (14)
Median BEV duration, months (95% CI)		12.5 (10.3–13.6)	13.5 (12.4–13.8)	13.8 (12.6–14.0)	13.4 (11.6–14.3)
BEV discontinued		67 (63)	176 (53)	118 (50)	60 (54)
Main reason for discontinuing BEV	Disease progression	23 (21)	42 (13)	44 (19)	20 (18)
	Treatment-related AE[a]	13 (12)	27 (8)	16 (7)	9 (8)
	Death	1 (1)	14 (4)	2 (1)	2 (2)
	Pt request	6 (6)	17 (5)	17 (7)	6 (5)
	End of documentation period	13 (12)	33 (10)	21 (9)	12 (11)
Grade 3/4 adverse events	All	45 (42)	113 (34)	87 (37)	44 (39)
	Serious	27 (25)	60 (18)	43 (18)	23 (21)
	Leading to BEV discontinuation	11 (10)	27 (8)	20 (8)	8 (7)
Median PFS, months (95% CI)[b]		19.4 (16.0–21.7)	21.8 (19.9–25.1)	22.6 (20.8–26.5)	18.6 (16.6–22.2)

[a]Reported as 'side effects of therapy' until Aug 2013.
[b]Data cutoff for interim analysis: 31 Jan 2017; events in 352 pts (45%). ECOG= Eastern Cooperative Oncology Group.

subgroups with BMI ≤20 (hazard ratio [HR] 1.27; 95% CI 0.92–1.77) or ≥ 30 (HR 1.33; 95% CI 0.98–1.81) vs > 20–25 kg/m^2 (Cox regression model) but in pts with a BMI ≤20 kg/m^2, numerically more grade 3/4 and serious adverse events were observed.

Conclusions: In these post hoc exploratory analyses we were unable to identify any clear effect of BMI on PFS. The tolerability of BEV + systemic CT for advanced OC appeared to be influenced by BMI.

Clinical trial identification: NCT01697488

Legal entity responsible for the study: Roche Pharma AG

Funding: Roche Pharma AG

Disclosure: J. Sehouli: Membership on advisory board or board of directors: AstraZeneca, Roche, OBI Pharma, Pfizer, Clovis, NovoCure. A. Mustea: Membership on advisory board or board of directors: Roche. S. Klawitter, A. Wegenaer: Employment: Roche Pharma AG. P. Wimberger: Membership on advisory board or board of directors: Roche, Novartis, Amgen, AstraZeneca, MSD, TEVA, PharmaMar, Fresenius Biotech; Corporate-sponsored research: Roche, Novartis, Amgen, Fresenius Biotech, MSD. All other authors have declared no conflicts of interest.

959P A prospective study to evaluate the role of Cytoreductive surgery (CRS)+ HIPEC in advanced epithelian ovarian malignancy -100 consecutive cases -INDIAN experience

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Background: To study the outcome and role of cytoreductive surgery (CRS) + HIPEC in advanced upfront and recurrent epithelial ovarian cancer.

Methods: 100 consecutive patients with advanced epithelial ovarian cancer diagnosed between January 2011 to January 2017 were included in study after informed consent. IRB ethical clearance was obtained. All patients underwent CRS followed by HIPEC with dedicated machine (PERFORMER-HT) using only cisplatin 45mg/l for upfront and cisplatin 45mg/l and adriamycin 15mg/l in recurrent cases for 90 minutes in semi-open technique at 42 degrees Celsius. Descriptive study statistical analysis was done.

Results: Out of 100 patients, 74 were primary and 26 recurrent. Of 74 cases, 67.5% (n = 50) had upfront CRS+ HIPEC and 32.5% (n = 24) had interval CRS + HIPEC. Of 26 recurrent, 69.3% (n = 18) were platinum sensitive and 30.7% (n = 8) were platinum resistant. Median age 54.5(22-78) PCI 11.9(5-37) duration of surgery 9.5hrs (5-15),GI recovery 5.4 days, hospital stay 11.4 days. 12% (grade III) adverse morbidity and 3% 60 day mortality. Prolonged duration of surgery (p = 0.001), multivisceral resection (p = 0.039) hypoalbuminemia (p = 0.04) hypocalcemia (p = 0.01) were predictive factors for morbidity and prolonged hospital stay. With a median follow up of 50 months we had 6 systemic (3 lymph node, 2 bowel surface and 1 liver parenchyma) and 6 peritoneal recurrence and 7 deaths. Over all survival in primary was 70 months, platinum sensitive 32 months and platinum resistant 12 months.

Conclusions: CRS+HIPEC in advanced epithelial ovarian cancer can be done with accepted morbidity and mortality. Multivisceral resection, prolonged surgery, hypoalbuminemia, hypocalcemia were predictive factors for morbidity and prolonged hospital stay. Primary ovarian malignancies and platinum sensitive benefit the most with CRS + HIPEC whereas platinum resistant disease does not have any benefit.

Legal entity responsible for the study: IRB ethical clerance, institional ethical board clerance

Funding: None

Disclosure: All authors have declared no conflicts of interest.

960P Role of laparotomy-based parameters in assessment of optimal primary debulking surgery and long-term outcomes in patients with stage iiic epithelial ovarian cancer

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Background: We evaluated the ability of our newly developed laparotomy-based model to predict optimal primary debulking surgery (PDS) and long-term outcomes of stage IIIC epithelial ovarian cancer (EOC).

Methods: Data of 400 IIIC EOC patients who underwent laparotomy were retrospectively analyzed to investigate predictors of optimal PDS. Parameters including infiltration of the bowel, peritoneum, diaphragm, hepatic surface, spleen, and stomach; omental caking; mesenteric retraction; and metastasis of the pelvic and para-aortic lymph nodes increased the difficulty of surgery. The parameters with a specificity ≥75%, positive predictive value ≥50%, and negative predictive value ≥50% were included in the final predictive index value (PIV) model. Each parameter was assigned a score based on the strength of its statistical association, and a total PIV was tabulated for each patient. Receiver operating characteristic (ROC) curve analysis was performed to assess the predictive ability of the model. Subgroup analyses were performed in patients with RD > 1 cm and ≤1 cm.

Results: After PDS, 223 (55.8%) patients with RD ≤ 1 cm had longer progression-free survival (PFS) and overall survival (OS) than patients with RD > 1 cm (PFS: 24.3 vs. 15.9 months; P < 0.001 and OS: 48.6 vs. 35.6 months; P < 0.001). Nine parameters (excluding pelvic lymph node metastasis) were assigned a PIV of 2. Patients with a PIV of ≥ 14 were more likely to undergo suboptimal PDS with a specificity of 100%. The area under the ROC curve of our PIV model was 0.753. Among patients with RD ≤ 1 cm, those with a PIV <2 had longer PFS and OS. Among patients with RD of > 1 cm, those who were sensitive to platinum had longer PFS and OS, there was no difference in PFS and OS between patients with and without combined multiple-organ resection, and the median PFS of patients with a lymph node rate of > 32.5% was shorter than in patients who did not undergo lymph node dissection, but the difference in OS was not significant.

Conclusions: When PDS left RD of ≤ 1 cm, patients with a PIV of < 2 had a better prognosis. When PDS left RD of > 1 cm, patients who were sensitive to platinum had a better prognosis. Additionally, patients with a lymph node rate of > 32.5% were more likely to progress.

Legal entity responsible for the study: no

Funding: None

Disclosure: All authors have declared no conflicts of interest.

961P ICON7: Ovarian cancer, platinum second-line chemotherapy and overall survival

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Background: The ICON7 trial reported increased progression-free survival with bevacizumab (bev) added to platinum-based chemotherapy in newly-diagnosed ovarian cancer, and increased overall survival (OS) in a poor prognosis subset. Most patients (pts) had further chemotherapy following progression. On average, pts receiving bev had later progression and were thus more likely to receive further platinum. We investigated the effect of second-line treatment type on the association between first-line bev and OS.

Methods: Second line chemotherapy regimens were categorised as platinum-containing or other. Platinum reuse varied with time to progression after end of 1st line (excl. maintenance bev) and also varied between centres. We categorised centres as high or low platinum use, from the proportion of their pts progressing in 0-8 months (mths) and retreated with platinum. The association between 1st line bev and OS was analysed separately at low-use centres and at high-use centres. Standard survival analysis techniques and methods appropriate for data with non-proportional hazards were used.

Results: ICON7 randomised 1528 pts 1:1 to reference treatment +/- bev. Reference pts were more likely to experience disease progression ≤8 mths (38% v 24%). Reuse of platinum varied with time to progression; 37% at 0-5 mths; 76% at 6-8 mths; 94% at ≥ 9 mths. 174 centres (covering 1290 pts) had ≥1 progression at 0-8 mths, 76 centres were classed low-use (<50% platinum 2nd line in 0-8mths) and 98 high-use. The earlier progression of reference pts resulted in fewer getting 2nd line platinum at low use centres (41% v 56%), but not at high-use centres (76% v 77%). There was evidence of significantly shorter OS among reference pts at low-use centres ($p = 0.05$, restricted mean survival 44.1 v 49.0 mths), but not at high-use centres ($p = 0.20$, restricted mean survival 52.2 v 50.0 mths).

Conclusions: Improved OS with bevacizumab may result from an association with platinum-containing second line treatment: bev increases time to progression, increased time to progression increases the likelihood of second line platinum, second line platinum increases OS. It is possible therefore that OS might be improved by a lower time threshold for second line platinum chemotherapy, whether or not bevacizumab has been used.

Clinical trial identification: ISRCTN: 91273375

Legal entity responsible for the study: ICON7 was a GCIG trial, overall sponsor is Medical Research Council, UK.

Funding: Medical Research Council Clinical Trials Unit at University College London

Disclosure: All authors have declared no conflicts of interest.

962P Disease burden during the "watchful waiting" period in patients with recurrent ovarian cancer

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Background: The standard of care for patients (pts) with recurrent ovarian cancer (OC) who respond to platinum-based chemotherapy has been "watchful waiting". While studies have shown that pts experience anxiety and fear of recurrence during watchful waiting, the rate of serious clinical events that require hospitalizations or emergency room (ER) visits during this observation period has not been examined. The objective of this study was to assess the rate of such events using a claims database.

Methods: This retrospective study identified pts newly diagnosed with OC in January 2009 to September 2015 in MarketScan® Commercial and Medicare Supplemental Databases (US). Pts with commercial or Medicare coverage for 12 months prior to and ≥1 month after first diagnosis were included. Recurrence was defined by the presence of 2nd-line platinum-based therapy, and watchful waiting as the period without active treatment following chemotherapy. Rate of inpatient admissions and ER visits during watchful waiting were assessed.

Results: 1312 pts were identified who had a treatment-free interval after 2nd-line platinum treatment. During this watchful waiting period (median duration, 162 days), 30.1% had an inpatient admission and 27.4% had an ER visit. Median time to first hospitalization from end of 2nd-line chemotherapy was 56 days, and median time to first ER visit was 68 days. There was a total of 650 inpatient hospitalizations, for an average of 0.5 per pt. Mean length of stay per hospitalization was 10 days. Top 5 reasons for hospitalizations were (1) intestinal obstruction without mention of hernia (13.5%), (2) secondary malignant neoplasm of respiratory and digestive systems (10.5%), (3) malignant neoplasm of ovary and other uterine adnexa (9.2%), (4) septicemia (4.5%), and (5) secondary malignant neoplasm of other specified sites (4.2%).

Conclusions: A substantial proportion of 2nd-line recurrent OC pts were hospitalized or had ER visits during the watchful waiting period post platinum treatment. The timing of these hospitalizations suggests that they were not necessarily related to progression but rather reflective of the ongoing disease burden patients experience during this "waiting" period.

Clinical trial identification: NCT01847274

Legal entity responsible for the study: TESARO, Inc.

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Disclosure: B. Harrow, K. Travers, M. Bala: Employment: Tesaro; Stock: Tesaro. B. Davis, A. Gilligan: Employment: Truven Health Analytics. All other authors have declared no conflicts of interest.

963P Impact of chemotherapy (CT) in heavily pretreated BRCA1/2 mutation carrier ovarian cancer (BMCOC) patients (pts)

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Background: Hallmarks of BMCOC are increased sensitivity to platinum-based CT (PCT) and PARP inhibitors (PARPi). Regulatory approvals of PARPi will affect CT strategies for heavily pretreated BMCOC pts. Effectiveness of CT in this population is investigated.

Methods: BMCOC pts who received CT from 2006-2016 at 4 cancer centers in Spain were retrospectively selected. OS and time to progression (TTP) were calculated with Kaplan Meier and Cox models.

Results: Out of 135 BMCOC pts identified (63% BRCA1; 37% BRCA2; 6 pts somatic), 87 (64%) had recurrent disease. After a median follow-up of 6 years, OS rate was 67% in BRCA1 and 66% in BRCA2 pts ($p = 0.98$). Median treatment lines after relapse was 4 (2-7); 42 pts (48%) were exposed to PARPi. At 3rd relapse, 78% pts remained platinum-sensitive (P-S). Out of 156 treatments given to 57 pts who had ≥3 treatment lines, 44% were PCT, 27% non-PCT, 14% PARPi and 15% PCT plus PARPi. Across all treatment lines, median TTP was 10.2 m (CI95% 8.4-11.9). In P-S context, TTP was improved with PCT plus PARPi (17.1 m), PCT (12.6 m) or PARPi (12.4 m) vs non-PCT (4.9 m, $p < 0.01$ all comparisons). We found longer TTP with Taxane/PCT compared with Gemcitabine/PCT (HR 4.0; CI95% 1.3-12.6, $p = 0.02$) and PLD/PCT (HR 3.8; CI95% 1.5-10.0, $p = 0.006$) in a model adjusted for treatment line. In platinum-resistant (P-R) setting, TTP was not significantly different with PCT (5.3 m) or PARPi (7.4 m) vs non-PCT (4.6 m, $p = 0.99$). For treatments administered beyond PARPi ($n = 27$), median TTP was not different with PCT in P-S (5.6 m) or PCT in P-R (4.1 m) vs. non-PCT (3.0 m, $p > 0.4$ all comparisons). Multivariate model (BRCA1/2 status, treatment line and prior PARPi) confirmed platinum sensitivity as the strongest predictor for longer TTP beyond 2nd relapse (*HR 0.28*; $p < 0.001$).

Conclusions: Heavily pretreated BMCC demonstrated increased CT sensitivity, including for non-PCT choices. In P-S setting, either PCT rechallenge (+/- PARPi) or PARPi monotherapy represent the best treatments options. PARPi exposure does not compromise benefit to subsequent CT. In this population, platinum-sensitivity remains the main prognostic factor to predict CT benefit.

Legal entity responsible for the study: Vall d'Hebron University Hospital Institute of Oncology (VHIO)

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964P Modeling and impact of organ function on the population pharmacokinetics (PK) of niraparib, a selective poly (ADP-Ribose) polymerase (PARP)-1 and -2 inhibitor

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Background: Niraparib (ZEJULA™) is a selective PARP-1 and -2 inhibitor approved for maintenance treatment in adults with recurrent ovarian cancer in complete or partial response to platinum-based chemotherapy. We developed a population PK (PPK) model for niraparib and determined the impact of hepatic and renal organ impairment on niraparib exposure.

Methods: Data from the phase 1 dose escalation and expansion (dose ranging from 30 to 400 mg once daily [qd]) and phase 3 ENGOT-OV16/NOVA (300 mg qd) studies were modeled using a compartmental population approach within nonlinear mixed-effects modeling (NONMEM). Patients (pts) who received a dose of niraparib were included in the PK analysis. The PPK base model was built using NONMEM techniques from the phase 1 study. The impact of pt variables (age, race, ethnicity, body weight), renal impairment (normal, mild, or moderate, based on serum creatinine clearance) and hepatic function (baseline serum alanine and aspartate aminotransferase, albumin, total bilirubin) on niraparib PK parameters was evaluated. A step-wise elimination procedure for each covariate was used to develop the final model. Model evaluation was performed via a visual predictive check.

Results: 512 pts (33–83 years old) were available for PK analysis (4109 measurements) from the phase 1 (n = 104) and phase 3 (n = 408) studies. A 2-compartment model (2CM) with first-order absorption and elimination best described the niraparib PK. In the base model, the typical value for niraparib apparent clearance was 16.2 L/h, with interindividual variability of 52.6%. The estimated volume of distribution was 1074 L (290 L central and 784 L peripheral compartment. Model diagnostics showed good agreement between predicted and observed individual niraparib plasma concentrations. No patient variables impacted niraparib PK. Neither the mild to moderate renal impairment nor the mild hepatic impairment significantly altered niraparib PK.

Conclusions: Niraparib disposition was best described by a 2-compartment model with moderate to high interindividual variability. Mild to moderate organ impairment did not significantly impact niraparib PK; no dose adjustments are recommended.

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Legal entity responsible for the study: Tesaro, Inc.

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Disclosure: Z-Y. Zhang, X. Wang, J. Wang, V. Kansra: Employment: Tesaro; Stock: Tesaro. H.S. Pentikis: Advisory board or board of directors: Tesaro; Consulting: Tesaro.

965P Evaluation of tumour responses and olaparib efficacy in platinum-sensitive relapsed ovarian cancer (PSROC) patients (pts) with or without measurable disease in the SOLO2 trial (ENGOT Ov-21)

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Background: In SOLO2 (NCT01874353), maintenance therapy with olaparib (Lynparza) significantly prolonged progression-free survival (PFS) vs placebo in pts with PSROC and a *BRCA1/2* mutation (*BRCA*m; hazard ratio 0.30, 95% CI 0.22–0.41; $P<0.0001$; Pujade-Lauraine *et al.* SGO 2017). Response rates achieved in SOLO2 are reported here for the first time, in addition to PFS outcomes grouped by pts' response to their most recent platinum-based chemotherapy (PBC) regimen (complete response [CR] or partial response [PR]).

Methods: The randomized, double-blind, Phase III SOLO2 study enrolled 295 pts previously treated with ≥2 PBC regimens who were in response after receiving their most recent cycle of PBC. Pts were randomized 2:1 to receive olaparib (300 mg bid; tablet) or placebo. Objective tumour responses were investigator assessed using modified Response Evaluation Criteria in Solid Tumors v1.1.

Results:

Table: 965P PFS subgroup analysis for pts with CR or PR at study entry

	Olaparib N = 196*	Placebo N = 99
Pts with CR at study entry		
n	91	47
Median PFS, months	NR	5.6
HR (95% CI)	0.26 (0.16–0.42)	
Pts with PR at study entry		
n	105	52
Median PFS, months	13.8	5.5
HR (95% CI)	0.37 (0.25–0.54)	

*One patient in the olaparib arm did not receive study treatment.
HR, hazard ratio; NR, not reached

At study entry, 73/196 (37%) olaparib pts and 35/99 (35%) placebo pts had measurable disease (evidence of target lesions at baseline); within this group, the adjusted objective response rate (number of pts with CR and PR divided by the number of pts with measurable disease at baseline) was 41.1% with olaparib vs 17.1% with placebo (odds ratio 3.52, 95% CI 1.34–10.59; P=0.0097). The placebo value is higher than expected, possibly due to a carry-over effect from last chemotherapy. In the olaparib arm, 17/113 pts (15.0%) with evidence of disease at baseline achieved CR following maintenance therapy (placebo arm, 5/55 [9.1%]).

Conclusions: Treatment with olaparib not only maintained the response achieved with PBC, but also induced additional antitumour activity in pts with measurable target tumour lesions at baseline. Olaparib monotherapy led to a significant PFS benefit in pts with both CR or PR at study entry, further supporting the role of olaparib as maintenance treatment for pts with PSROC and a *BRCA*m.

Clinical trial identification: NCT01874353, 1 June 2017

Legal entity responsible for the study: AstraZeneca

Funding: AstraZeneca

Disclosure: J. Ledermann: Honoraria from AstraZeneca and Pfizer, consulting fees from AstraZeneca, Clovis Oncology, Pfizer and Roche. N. Lainez Milagro: Advisory board for AstraZeneca. C. Scott: Received honoraria from Roche, research funding from Roche, Genentech and Clovis Oncology, royalties to the institution from AbbVie, and travel and accommodation expenses from Roche and AstraZeneca. P. Harter: Advisory boards for AstraZeneca, Clovis, Pharmamar, Roche and Tesaro, and lecture fees from AstraZeneca and Roche. T. Enomoto: Lecture fees from Chugai, AstraZeneca, Kaken, Johnson & Johnson, Nihonkayaku and Mochida. G.S. Sonke: Institutional research funding by AstraZeneca, Merck, Novartis and Roche. A. Allen: Employee of AstraZeneca. E. Pujade-Lauraine: E. Pujade-Lauraine has received advisory board membership and honoraria from AstraZeneca and Pfizer, and advisory board membership, honoraria and speakers' bureau membership from Roche. All other authors have declared no conflicts of interest.

966P Outcomes of the combination trabectedin and pegylated liposomal doxorubicin (T-PLD) in recurrent platinum-sensitive ovarian cancer (OC): a GINECO cohort study

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Background: T-PLD is an effective alternative for the treatment of recurrent platinum-sensitive OC, especially in the partially platinum-sensitive population with a platinum-

free interval (PFI) of 6-12 months. The aim of this work was to assess the clinical impact of the combination when used in routine practice.

Methods: This was a prospective, multicenter study carried out in 25 French centers. Eligible patients (pts) were women ≥18 years old with histologically proven relapsed disease following at least one platinum-based chemotherapy and candidates to receive T (1.1 mg/m^2) plus PLD (30 mg/m^2). Analysis were performed according to the PFI subgroups (PFI 6-12 and PFI>12 [fully platinum-sensitive]) using Stata and R software.

Results: From 07/2014 to 06/2016, 91 pts with platinum-sensitive OC were included (median age 65 years-old, range: 42-86). Most pts had PFI 6-12 (n = 58; 63.7%) vs. n = 33 with PFI>12. Pts were treated with a median of 6 cycles (range: 1-12) of T-PLD. 47 (51.6%) pts received T-PLD as ≥ 3rd line of chemotherapy (range: 2-8). The toxicity profile in the PFI subgroups was not different from that of the overall population. The number of pts with grade 3/4 hematological toxicities in the PFI 6-12 and PFI>12 cohorts was: neutropenia 29.6%/17.6%, febrile neutropenia 4.4%/3.3%, thrombocytopenia 7.7%/12.1%, anemia 5.5%/2.2%. Grade 3 hand and foot syndrome (1 pt) and mucositis (1 pt) were observed in the PFI 6-12 group. Increases in transaminases (grade 3/4) were experienced by 11 pts (10/1) in the PFI 6-12 group and by 5 pts (4/1) in the PFI>12 group. 3 patients in the PFI 6-12 group and 3 in the PFI>12 group discontinued treatment because of toxicities, 6 and 2 due to premature death. Partial and complete responses were achieved in 43 pts (PFI 6-12: n = 26; PFI>12: n = 17, p = 0.82). Median PFS after T-PLD was 5.9 months (95%CI 4.9-6.7) in the PFI 6-12 group and 5.8 months (95%CI 3.7-8.5, logrank p = 0.37) in the PFI>12 group. OS data were not mature at the time of this analysis.

Conclusions: The safety profile of T-PLD when used in real-life management of non-selected OC pts is similar to that observed in clinical trials. T-PLD remains a valuable option to pts with both partially and fully platinum-sensitive disease.

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Legal entity responsible for the study: ARCAGY-GINECO

Funding: PharmaMar

Disclosure: L. Gladieff: PharmaMar fees in 2015 and 2016. All other authors have declared no conflicts of interest.

967P An observational, multicenter, prospective study of trabectedin plus pegylated liposomal doxorubicin (PLD) in patients with platinum-sensitive recurrent ovarian cancer (PSROC)

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Background: The OVA-YOND prospective non-interventional phase IV study evaluated trabectedin plus PLD in real-life clinical practice to assess the toxicity and efficacy of the combination when given in accordance with the marketing authorization to women with PSROC.

Methods: Data from patients treated with PLD 30 mg/m^2 and immediately followed by trabectedin 1.1 mg/m^2 3-h i.v. infusion every 3 weeks have been collected.

Results: From 02/2013 to 12/2016, 77 enrolled patients from 31 sites across Germany who received at least one cycle of trabectedin plus PLD were evaluated. All patients had a platinum-sensitive relapse with a median platinum-free interval of 12 months (range: 6-86 months). Median age of patients was 66 years (range: 40-78) and 80.5% had ECOG performance status 0/1. Serous carcinoma was the most prevalent histological type (n = 54; 70.1%), tumor was localized at the ovary in 88.3% of patients and 38 patients (49.4%) were diagnosed with FIGO IIIC stage. Median number of trabectedin plus PLD cycles received per patient was 6, with 39 patients (50.6%) receiving ≥6 cycles and up to a maximum of 21 cycles. Median treatment duration was 4.24 months, mostly on an outpatient basis (≥66.7-100% of cases). Five patients (6.5%) had a complete response and 19 patients (24.7%) achieved a partial response for an ORR of 31.2% with a median duration of 6.25 months. Additionally, 16 patients (20.8%) had disease stabilization for a disease control rate of 51.9%. With 64 PFS events recorded, median PFS was 6.3 months (CI95%: 5.1-7.3) and median OS was 16.4 months (CI95%: 11.3-19.3). A total of 278 trabectedin-related adverse events (TRAE) occurred in 57.1% of the patients who recovered in 70.9% cases. Most common grade 3/4 TRAE were leukopenia (18.2% of patients), neutropenia (15.6%), thrombocytopenia (9.1%), ALT (7.8%) and AST (6.5%) increase, and nausea/vomiting (5.2% each). No grade 5 or unexpected TRAE occurred.

Conclusions: Trabectedin plus PLD confer clinically meaningful benefit to patients with PSROC, being either comparable or better to those previously observed in selected population from clinical trials or other real-life studies, and with a manageable safety profile.

Clinical trial identification: NCT01869400; OVA-YOND

Legal entity responsible for the study: PharmaMar

Funding: PharmaMar

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968P PRO-002, a phase Ib dose-escalation study of NUC-1031 with carboplatin for recurrent ovarian cancer

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Background: NUC-1031 (Acelarin) is a first-in-class nucleotide analogue that overcomes key cancer cell resistance mechanisms to generate high intracellular levels of dFdCTP. In the PRO-001 study, single agent NUC-1031 achieved impressive clinical activity across multiple solid tumors. In this PRO-002 study, NUC-1031 was combined with carboplatin in 25 pts with recurrent ovarian cancer (OC).

Methods: NUC-1031 was administered in a dose-escalation schedule as a 30-min infusion on days 1 & 8 with carboplatin on day 1, every 3 weeks for ≤6 cycles. Four dose cohorts of NUC-1031 (500, 625 and 750 mg/m^2) with carboplatin (AUC4 or 5) were studied. The primary endpoint was to determine RP2D. Secondary endpoints included safety, RECIST response, PFS and PK/PD.

Results: 25 pts (median age 64 yrs) participated, having received a median of 3 (range 2-6) prior lines of therapy. All had received prior platinum regimens (10 had prior carboplatin + gemcitabine). 23 pts were response-evaluable, of whom 7 were platinum refractory, 10 were platinum resistant, 4 were partially platinum sensitive and 2 were platinum sensitive. Strong efficacy signals were achieved with 1 unconfirmed CR at the end of treatment (4%), 8 PRs (35%, 4 confirmed), 12 SDs (52%, 10 confirmed) and 2 PD (9%). Median PFS was 7.4 months (range 1.2-11.2). The combination regimen was well tolerated. 5 DLTs occurred in 4 pts: 2 Grade (G) 4 thrombocytopenia; 2 G3 fatigue and 1 G4 neutropenia. No DLTs occurred in the NUC-1031 500 mg/m^2 + carboplatin AUC5 group. 7 pts reported treatment-related SAEs. The most common SAE was thrombocytopenia, reported in 3 pts. NUC-1031 was stable in plasma (apparent $t_{1/2}$=3.8 h). Combination with carboplatin rapidly generated very high intracellular dFdCTP levels (C_{max}=12.1 μM/mg, TP/500 mg/m^2 and T_{max}=30 min) that were maintained for 24 h.

Conclusions: NUC-1031 combined with carboplatin is well tolerated and effective in recurrent platinum resistant and sensitive OC. dFdCTP levels were increased 25% by the addition of carboplatin. The RP2D was 500 mg/m^2 NUC-1031 on days 1 & 8 with AUC5 carboplatin day 1, q21d. The efficacy and synergy of this schedule and the ability to deliver carboplatin at AUC5 makes this an attractive therapeutic combination.

Clinical trial identification: NCT02303912

Legal entity responsible for the study: Nucana Biomed

Funding: Nucana Biomed

Disclosure: S.P. Blagden: Acted on advisory boards for Novartis and Clovis Oncology and has directorship of RNA Guardian Ltd. S. Nicum: Consultant/Advisory Boards: Roche, AstraZeneca, Abbvie, Tesaro, Clovis Speaker: AstraZeneca, Roche Clinical Trials Sponsored: AstraZeneca. D.J. Harrison: DJH has a research consultancy and research sponsored by Nucana Biomed. Family member has stock options with Nucana Biomed. All other authors have declared no conflicts of interest.

969P Phase 1/2 trials of peptides cocktail vaccine for resistant cervical and ovarian cancer: QoI analysis

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Background: We conducted phase 2(P2) studies of peptides vaccine (PV) immunotherapy for cervical (CC) and ovarian cancer (OC) using HLA-restricted tumor specific peptides and VEGF receptor 1 (R1)and 2(R2). All HLA0201(A02) and 2402 (A24) restricted peptides used were found from human CC and OC, respectively in GMP grade. The P1 showed feasible (presented in ECCO2013), and further P2 had completed in 66 accruals and the results showed efficacy (ASCO2015 5567). Approval of IRB had obtained. This time, QOL study using GOG FACT-O had analyzed and survival data were up-dated.

Methods: Heavily treated CC and OC with A24 or A02 within ECOG PS 2 were candidate. Fully written-IC had obtained. PV cocktails were as follows: for OC of A24 comprised FOXM1, MELK, HJURP, VEGFR1(R1) and R2. As for OC A02, PV comprised HIG2, R1 and R2. For CC of A24, it comprised of FOXM1, MELK and HJURP, and CC with A02, it comprised of URLC10 and HIG2. Each peptide was mixed at a dose of 1mg with adjuvant, MONTANIDE in total 1ml. Vaccination schedule included 12 subcutaneous weekly injections followed with additional 8 administrations (adm.) in two-week intervals and more 8 adm. in 1 month (m) intervals were performed. At pre- and every 8th post-adm., QOL sheet was obtained.

Results: PV was well tolerated with no major adverse events (AEs), and during first 8 adm. AEs had caused by prior-chemotherapy/radiotherapy (after 1 month (m) washout) had been improved. As for QOL, physical-, functional- social-, and mental QOL were getting preferable during first 16 adm., however, during longer observation beyond 3 m they were deteriorated gradually due to disease progression. The final mOS of CC and OV was 4.9 m + (0.6-76.6m+) and 7.2m(1.1-59.1m), respectively. As for

prognostic factors, significant benefits were seen among lower c-reactive protein (CRP), higher levels of peripheral lymphocytes count, younger age, and smaller residual tumors at baseline. They were strongly rerated to good QOL in $p < 0.003$ or more by Wilcoxon signed rank test.

Conclusions: This PV immunotherapy had efficacy not only in safeness, response, and overall survival, but also in maintenance of QOL in this cohort of patients Further PV trials for other cohorts such as adjuvant therapy would be warranted.

Clinical trial identification: UMIN:000003860, 000003862, 000003902, 000003902

Legal entity responsible for the study: Captivation

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970P A phase 1 study of selinexor (S) in combination with paclitaxel (P) and carboplatin (C) in patients (pts) with advanced ovarian (OC) or endometrial cancers (EC)

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Background: Selinexor (S) is an oral, first in class, inhibitor of exportin 1 (XPO1). In a Phase II clinical trial of pts with relapsed ovary cancer (OC) andendometrial cancer (EC), single agent S, demonstrated anti-cancer activity. In addition, clinical exploratory analysis has demonstrated S target engagement and a relationship between baseline circulating tumor cells and duration of response. Here we report results of a phase 1 study evaluating safety/tolerability of S combined with C and P in pts with advanced OC and EC or carcinosarcomas.

Methods: Patients (Pts) were enrolled using 3 + 3 dose escalation design for each regimen (reg). All pts with OC received 1 prior platinum (plt) therapy. Ptswith EC could be chemotherapy naïve or have received 1 prior plt therapy. Pts were enrolled to 1 of 4 regimens regardless of disease type as described in Table. Response was evaluated Q9 weeks (RECIST 1.1).

Results: 16 pts (12 EC, 3 OC, 1 endometrial carcinoma) were enrolled. 1 drug related DLT of G3 syncope occurred on Reg 2. Most common G2 AEs were hyperglycemia (43.8%), leukopenia (43.8%), anemia (31.3%). Most common Grade 3 and 4 AEs were anemia (62.5%), neutropenia (37.5%), lymphopenia (43.8%), neutropenia (31.3%) thrombocytopenia (12.5%). 50% of evaluable pts on Reg 1 and 2 were dose reduced due to S toxicity. One dose reduction of S on Reg 3. There were no dose reductions on Reg 4. 13 pts were evauble for efficacy: 2 CRs, 10 PRs, and 1 SD. Time on study ranged from 2–10.8 mos with 3 pts still on study.

Conclusions: Selinexor in combination with carboplatin and paclitacel (CP) chemotherapy in advanced OC, EC, and carcinosarcomas was well tolerated. The RP2Ds have been established at 30mg/m^{2}twice weekly of S and 60 mg flat dose weekly in combination with CP chemotherapy. Given encouraging response, expansion cohorts for Regs 3/4 are planned. Frequent molecular alterations seen in the EC pts included: TP53, PIK3CA, and KRAS. Evaluation of S target engagement/correlatives of response will be discussed.

Table: 970P

Regimen #	N	Regimen details
1	4	C AUC5 (day 1), P 175 mg/m^2 (day 1) and S 30 mg/m^2 (days 1, 4, 8, 11, 15, 18)
2	6	C AUC5 (day 1), P 80 mg/m^2 (days 1, 8, 15) and S 30 mg/m^2 (days 1, 4, 8, 11, 15, 18)
3	3	C AUC5 (day 1), P 80 mg/m^2 (days 1, 8, 15) and S 60 mg (days 1, 8, 15)
4	3	C AUC5 (day 1), P 175 mg/m^2 (day 1) and S 60 mg (days 1, 8, 15)

Clinical trial identification: NCT02269293

Legal entity responsible for the study: Memorial Sloan Kettering Cancer Center

Funding: Karyopharm Pharmaceuticals

Disclosure: All authors have declared no conflicts of interest.

971P Pazopanib and oral cyclophosphamide in women with platinum resistant epithelial ovarian cancers

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Background: Women with recurrent, multiply treated epithelial ovarian cancer (EOC) have unfavorable prognosis with limited treatment options after failure of platinum based regimens. Antiangiogenic therapies have shown some efficacy in these patients. We report here a retrospective analysis of women with recurrent, platinum resistant EOC treated with an oral regimen of anti-angiogenic agent Pazopanib and Cyclophosphamide.

Methods: Women with histologically proven recurrent platinum-resistant EOC were treated with tablets pazopanib (600mg p.o. daily in two divided doses, 400 mg and 200 mg) and cyclophosphamide (50 mg p.o. daily for 14 days every 21 days) until disease progression or unacceptable toxicity. Response was evaluated radiologically every 12 weeks.

Results: Eighteen patients (16 platinum resistant and 2 platinum refractory) were treated between April 2014 and April 2017 with a mean age of 50 (38-60) years and median 4 (2- 8) previous lines of chemotherapy, including three patients with progressive disease on bevacizumab. Patients received a median of 6 (2-28) cycles of pazopanib and cyclophosphamide with partial response in 8 (44%) patients (including 1 of 3 prior bevacizumab treated patients), stable disease in 5 (28%) and disease progression in 5 (28%) patients, as best response. The median progression-free survival was 5.0 months. Common adverse events were fatigue (50%), diarrhea (50%), elevated liver enzymes (43%), mucositis (61%), myelosuppression (28%), Skin toxicity (33%), hypertension (6%) and hair depigmentation (6%). Dose reduction due to toxicity was required in 11 (61%) patients and no patient stopped treatment due to toxicity.

Conclusions: Pazopanib and oral cyclophosphamide is a well-tolerated regimen with clinically relevant benefit in platinum resistant, epithelial ovarian cancer patients.

Clinical trial identification: This is a retrospective analysis of Platinum resistant epithelial ovarian cancer patients treated at our instittute. The approval for doing this analysis was taken from Insitute s ethics committee.

Legal entity responsible for the study: Institutional Review Board Institutional Review Board, Tata Memorial Hospital, Mumbai, India

Funding: None

Disclosure: All authors have declared no conflicts of interest.

972P Apatinib as a salvage treatment in gynecologic cancer patients failed from two or more lines of prior chemotherapy

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Background: Apatinib is an oral inhibitor of the vascular endothelial growth factor receptor (VEGFR)-2. There is currently no standard treatment for patients with gynecologic cancer who failed from ≥2 lines of chemotherapy. The purpose of this study is to evaluate the benefits and adverse events of apatinib in the treatment of patients with advanced cervical and ovarian cancer who failed from ≥2 lines of chemotherapy.

Methods: Patients with advanced cervical and ovarian cancer received at least two lines of prior chemotherapy before being treated with apatinib were retrospectively reviewed between April 2015 and January 2017. All included patients received continuous apatinib treatment until disease progression, death, or intolerable toxicity. Prognosis and toxicities were evaluated by the Kaplan-Meier method and according to NCI-CTC 3.0, respectively.

Results: Twenty-six patients were eligible (cervical cancer, n = 12 (46.2%); ovarian cancer, n = 14 (53.8%)). After apatinib dose adjustment, 14 patients (53.8%) received 500 mg/day, 8 received 250 mg/day, 3 received 425 mg/day, and one received 675 mg/day. The median progression-free survival (PFS) of cervical and ovarian cancer was 8 months (95% confidence interval (CI): 3.83-12.17) and 4 months (95%CI:1.57-6.44), respectively. The objective response rates in cervical cancer and ovarian cancer were 50% (n = 6/12) and 50% (n = 7/14), respectively. The disease control rates were 100% (n = 12/12) for cervical cancer and 71.4% (n = 10/14) for ovarian cancer. No complete response was observed. The toxicities associated with apatinib were generally acceptable: eight patients (30.8%) developed grade 3/4 toxicity. The most common adverse events were hypertension (n = 17; 65.4%), hand-foot syndrome (n = 24, 92.3%), and mouth mucositis (n = 20, 76.9%).

Conclusions: Apatinib monotherapy could be a promising and tolerable treatment for patients with advanced/recurrent cervical and ovarian cancer who failed from two or more lines of chemotherapy.

Legal entity responsible for the study: Congying Xie

Funding: None

Disclosure: All authors have declared no conflicts of interest.

973P A GINECO phase II study of Navitoclax (ABT 263) in women with platinum resistant/refractory recurrent ovarian cancer (ROC)

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Background: Among ovarian cancer patients with early relapse after platinum chemotherapy, there is no convincing active treatment. In preclinical studies, we previously demonstrated promising activity of Navitoclax (ABT-263), an anti-apoptotic inhibitor of Bcl-2 family, in ROC tumors, suggesting a potential action in platinum resistant patients. In this prospective multicentric phase II study, we evaluated the efficacy of Navitoclax monotherapy in heavily pretreated ROC patients.

Methods: This study included high grade serous patients with platinum resistance. Navitoclax was orally administered at 150 mg/day during a lead in period (7 to 14 days) and then increased to 250 mg in the absence of dose-limiting thrombocytopenia (<G3). Treatment was continued until disease progression or toxicity. PFS was the primary endpoint. Response was assessed using RECIST criteria. Analyses of Bcl-2 family proteins were also planned.

Results: From January to September 2016, 47 patients were included in 13 institutions and 46 patients were analysed: 44 ovarian carcinomas, 1 peritoneal carcinoma and 1 fallopian tube, median age 63 (38-80); BRCA1/2 mutations (n = 7), negative (n = 25) and unknown (n = 14). The median number of prior treatment lines was 4 (2-12). PFS was 50 days [6-234] with 1 partial response (PR), 15 stable diseases (SD). Thrombocytopenia was the major expected side effect, with G3 (n = 11) and G4 (n = 1) leading to maintain the dose at 150 mg for 8 patients and to treatment discontinuation for 3 patients. Neither significant bleeding nor toxic death was observed. 26 patients were treated after progression, 23 with chemotherapy (10 receiving platinum agent): among the 21 evaluable patients, 1 PR and 8 SD were observed, including 6 patients treated with platinum, with 3 long responders (7 to 9 months). No BRCA mutation was observed among the responders.

Conclusions: Navitoclax monotherapy had modest activity without unacceptable toxicity. However, as shown by response to treatment after progression, Navitoclax may reverse platinum resistance in ROC patients. Complementary biological data in progress may help select patients who could benefit from Navitoclax.

Clinical trial identification: EudraCT number: 2015-000193-35 Clinical Trial Number: N° NCT02591095

Legal entity responsible for the study: Centre François Baclesse - CAEN

Funding: The French Cancer Research Hospital Program in 2011 & the Mariapia Bressan award in GINEGEPS 2014 Drug supply has been provided by Abbvie Laboratory

Disclosure: All authors have declared no conflicts of interest.

974P Reproductive function in patients (pts) with malignant ovarian germ cell tumors (MOGCT) following chemotherapy (ChT)

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Background: MOGCT generally affect young women, grow rapidly, usually involve one ovary and are highly chemosensitive. Only a few studies have evaluated the reproductive outcomes of pts following ChT. The aim of this study was analysis of long-term effects of ChT on reproductive function in a large population of young women treated for MOGCT in our center.

Methods: Inclusion criteria in our study were MOGCT, fertility-sparing surgery, cisplatin- and etoposide-based induction ChT (BEP/EP regimen), age under 40, no relapse following ChT at least 1 year. Blood tests were taken for hormones of ovarian function (follicle-stimulating hormone, luteinizing hormone, estradiol, anti-Müllerian hormone (AMH), inhibin B) to assess their menstrual, reproductive function, post therapeutic status of pregnancy or delivery.

Results: A total of 47/163 (28.8%) pts with MOGCT treated in our center between 1987-2015 satisfied to the criteria. Mean age was 21 years (range, 14-35). Median number of ChT cycles was 4 (range, 1-6). The 5-year OS was 85% for all pts and 100% for these 47 women. All pts recovered their menstrual function during the first year after completion of ChT. With median f.-up 90 mo. (range, 12-228), 23/47 (49%) pts attempted conception, 18/23 (78.3%) women conceived with 20 live birth deliveries. There were 2/18 (11%) miscarriages and 6/18 (33.3%) terminations. Four women were pregnant at the moment of the analysis. Inhibin B level was normal in all 15 evaluated pts (median 74,4 pg/ml, range 10-120). Median of AMH level was 0,97 ng/ml (range 0.08-6). In 10 (52.6%) of 19 pts AMH level was <1 ng/ml, that considered a decrease of ovarian reserve. The quantity of pregnancies and deliveries, levels of hormones didn't depend on the number of cycles.

Conclusions: Unilateral adnexectomy followed by modern cisplatin-based chemotherapy does not adversely affect young women's fertility and provides high chance for cure.

Legal entity responsible for the study: Russian Cancer Research Center

Funding: None

Disclosure: All authors have declared no conflicts of interest.

975P Preoperative MRI versus intra-operative frozen section in surgical management of clinically early endometrial cancer

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Background: The role of systematic lymphadenectomy in clinically early stage endometrial cancer is controversial. A number of factors can predict lymph node metastasis including myometrial invasion, tumor grade in endometrial cancers. The purpose of the present study is to evaluate the accuracy of preoperative MRI and intraoperative frozen section in determining the depth of myometrialinvasion, cervical involvement, tumor size and lymph nodal status. We also studied the accuracy of preoperative endometrial biopsy and intraoperative frozen section in determining the grade of the tumor.

Methods: Medical records of 160 consecutive cases of clinically early stage endometrial cancer were reviewed retrospectively. A record of depth of myometrial invasion, tumor size, cervical involvement and presence of enlarged lymph nodes was made on a preoperative MRI. Similar depth of myometrial invasion, tumor size, cervical involvement and grade of the tumor were recorded on an intraoperative frozen section. The grade of the tumor was also recorded on a preoperative endometrial biopsy. Standard statistical calculations were used.

Results: The sensitivity and specificity of MRI for myometrial invasion were 81.3 and 75%, respectively while that for frozen section were 80 and 96.2%, respectively. For tumor grade the sensitivity and specificity of preoperative endometrial biopsy were 60 and 95.6%, respectively while that of frozen section were 53.8 and 97.6%, respectively. For cervical involvement the sensitivity of MRI and frozen section was 62.5 and 98.4%, respectively.

Conclusions: Although the sensitivity of both frozen section and MRI for predicting deep myometrial invasion was similar (80 vs 81.3%) but the specificity (96.2 vs 75%) and negative predictive value (92.7 vs 88.2%) of frozen section were superior to MRI.Both preoperative biopsy and intraoperative frozen section had low sensitivity (60 vs 53.8%) for detecting a high-grade lesion.

Legal entity responsible for the study: Institutional ethics committee, Tata Memorial Centre

Funding: None

Disclosure: Author has declared no conflicts of interest.

976P Impact of the adjuvant management and risk factors on survival in FIGO stage 3 endometrial cancer patients

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Background: Patients with FIGO stage 3 endometrial cancer often receive adjuvant therapy, but level I evidence is lacking. The purpose of this study was to evaluate

Table: 976P

Survival	RFS (%) (p < 0.00001)		DFS (%) (p < 0.00001)		OS (%) (p < 0.00001)	
	5 year	10 year	5 year	10 year	5 year	10 year
No Tx	7 (1.2-42.7.3)	NA	5 (0.08-32.1)	NA	11 (3.8-31.3)	NA
CT	34.1(18.3-63.4)	34.1(18.3-63.4)	31.6(17.4-57.4)	23.7(10.4-53.9)	47.5(31.9-70.9)	26.7(13.3-53.9)
RT	37.7(23.8-59.7)	18.8(4.4-81.1)	34.1(21.1-55.2)	9.5(1.7-52.4)	47.8(33.2-68.8)	9.7(1.8-51.5)
Both	61.6(53.8-70.5)	40.8(24.2-68.6)	58.3(50.4-67.3)	36.8(21.0-61.8)	65.2(57.5-74)	38.1(24.4-59.6)

relapse-free survival (RFS), disease-free survival (DFS) and overall survival (OS) in patients with FIGO stage 3A to 3C2 patients by treatment modality received and risk factors.

Methods: Consecutive patients with FIGO stage 3 endometrial cancer treated from 2000-2010 were identified in the provincial cancer registry. Clinicopathologic characteristics, adjuvant treatments and outcomes were compared using descriptive and multivariable analyses.

Results: 261 patients had stage 3 endometrial cancer, 132 with stage 3A, 9 with 3B, 85 with 3C1 and 35 with 3C2. 39 had FIGO grade 1 disease; 73, grade 2; 147, grade 3. 160 had endometrioid and 35 had serous carcinoma. 170 (65%) had >50% myometrial invasion;162 (62%) had presence of LVI. 161 patients received both adjuvant chemotherapy (CT) and radiotherapy (RT); 33 received RT only; 32 received CT only; 35 received neither. 5-year (5Y) RFS, DFS and OS were similar among stage IIIA (RFS 55.1%, DFS 46.7%, OS 58.5%), IIIB (RFS 50.8%, DFS 50.8%, OS 58.5%), IIIC1 (RFS 45.4%, DFS 44%, OS 49.9%) and IIIC2 (RFS 42%, DFS 42%, OS 41.6%). Use of adjuvant RT was associated with improved median RFS (57.2 vs. 16.9m, $p < 0.00001$), DFS (53.7 vs 14.7m, $p < 0.00001$), and OS (61.9 vs 25.7m, $p < 0.00001$) compared to no RT. Likewise, use of adjuvant CT was also associated with improved RFS (58.4 vs 20.4m, $p < 0.00001$), DFS (54.8 vs 16.5m, $p < 0.00001$), and OS (62.9 vs 26.5m, $p < 0.00001$) compared to no CT. The Table below shows 5Y and 10Y survival outcomes by adjuvant treatment received. On multivariate analysis, older age, grade 3 disease, deep myometrial invasion >50%, and no adjuvant RT or CT were identified as adversely impacting RFS, DFS and OS.

Conclusions: In FIGO stage III endometrial cancer patients, use of both CT and RT is associated with improved RFS, DFS and OS and therefore should be recommended in all eligible patients after resection. 5Y RFS, DFS and OS are similar across stages IIIA to IIIC2. Risk factors including age, high grade and deep myometrial invasion are independent predictors of survival.

Legal entity responsible for the study: BC Cancer Agency

Funding: None

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977P Is chemotherapy worthwhile in patients with FIGO stage 1B, lymph nodes negative, grade 3 endometrial cancer?

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Background: FIGO stage 1b endometrial cancer represents a major treatment challenge and standard of care is still unclear.

Methods: From March 1996 to March 2016, we retrospectively collected patients diagnosed with endometrial cancer stage Ib (invasion ≥ 50% of the myometrium, 2009 FIGO staging), lymph nodes negative after lymphadenectomy, and grade 3. We performed descriptive analysis and Kaplan Meier test using SPSS 20.0.

Results: Overall, 39 consecutive patients have been collected (28 at the National Cancer Institute of Milan and 11 at the University Hospital of Udine). Median age was 65.8 years (range 35.6-84.9). Endometrioid adenocarcinoma was diagnosed in 32 patients (82.1%), 4 serous adenocarcinoma (10.3%), 2 papillary serous adenocarcinoma (5.1%), and 1 clear cell adenocarcinoma (2.6%). Taking into account only endometrioid histotype, 23 patients received adjuvant radiotherapy (RT): 13 patients (40.6%) received brachyRT, 7 patients (21.8%) received external RT, 3 patients (9.4%) received both; 13 patients underwent platinum-based adjuvant chemotherapy (CT): 7 patients only CT, 2 patients external RT followed by CT and 2 patients brachyRT followed by CT. After a median follow up of 45.8 months (range 27.3 -236.8), median disease-free survival was 23.3 months (range 4.7-157.4); 7 patients (21.9%) experienced disease relapse and 5 patients (15.6%) died due to endometrial cancer. Relapse rate was 21.7% in patients who received RT versus 22.2% who did not. To note, relapse rate was only 9.1% in patients who received CT versus 28.6% in patients who did not.

Conclusions: According to our study, patients with stage 1b, node negative, grade 3 endometrioid endometrial cancer seems to derive a great benefit from adjuvant chemotherapy. This data needs to be further investigated in a large prospective clinical trial.

Legal entity responsible for the study: Department of Gynecologic Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

Funding: None

Disclosure: All authors have declared no conflicts of interest.

978P Significance of MSH2 promoter methylation in endometrial cancer with MSH2 deficiency

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Background: Inactivation of MSH2 was frequently observed in endometrial cancer (EC) with microsatellite instability (MSI) or mismatch repair complex deficiency (dMMR). With respect to MSH2 deficiency (dMSH2), most of dMSH2 were caused by germline mutations in the MSH2 gene or EpCAM deletions. Meanwhile, heritable germline epimutations in MSH2 reported in a few Lynch syndrome families that lacked germline mutations in the MSH2 gene. We previously provided evidence for frequent MSH2 hypermethylation in Lynch syndrome colorectal tumors with dMSH2 and MSH2 methylation may serve as the "second hit" at the wild-type allele. Herein, we examined precise epigenetic alteration in MSH2 promoter and tried to reveal associations to family history of Lynch syndrome related tumors.

Methods: We analyzed MSH2 promoter methylation status, as well as MLH1 methylation status, and expression status of the mismatch repair proteins (MLH1, MSH2, PMS2, and MSH6) by immunohistochemistry in 326 EC patients. DNA was extracted from formalin-fixed, paraffin-embedded tissue, and analyzed MSI status by four mononucleotide markers and both MLH1 and MSH2 promoter methylation status by a fluorescent quantitative bisulfite PCR assay.

Results: MSI or dMMR was observed in 82 (25.2%) or 89 ECs (27.3%), respectively. ECs with dMSH2 were observed in 18 (5.5%) of 326 ECs (20.2% of dMMR). MSH2 promoter methylation was detected in 8 tumors (2.5% in 319 tumors excluding not available 7 ECs), and significantly correlated with dMSH2 ($P = 0.0072$, Fisher's exact probability test). Then, we also examined the family history of first-degree relatives. In this cohort, although patients with dMMR were significantly associated with family history of Lynch syndrome related tumor ($P = 0.0312$), patients with this family history are more frequently observed in patients with dMSH2 ($P = 0.0052$). Interestingly, patients with MSH2 promoter methylation were strongly associated with the family history of Lynch syndrome related tumor ($P = 0.0053$), though patients with MLH1 methylation were not ($P = 0.8345$).

Conclusions: MSH2 methylation significantly correlated with ECs with dMSH2 and may have strong relation with family history of Lynch syndrome related tumor, suggesting it takes a role as "second hit" to the MSH2 gene.

Legal entity responsible for the study: Takeshi Nagasaka

Funding: None

Disclosure: All authors have declared no conflicts of interest.

979P Achievement of complete response (CR) in metastatic or recurrent cervical cancer (MRCC): Does it matter?

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Background: MRCC is a devastating disease with poor long-term outcomes. Bevacizumab (BEV) added to chemotherapy (CT) improves significantly overall survival (OS) in MRCC patients (pts). Aim: to characterize clinic-pathologic features associated to CR and its impact on pts outcome.

Methods: Single-institution chart review of MRCC pts who were treated with 1st line CT between 2005 and 2016. CR was defined by Response Evaluation Criteria in Solid Tumors (RECIST v1). The prognostic and predictive value of clinic-pathologic features, was evaluated.

Results: Seventy-two pts (62% squamous; 30% adenocarcinoma; 8% others); with median age of 48 years (28-77) were selected. Forty-five pts (62%) had prior CT-radiation; 55 pts (79%) had recurrent/persistent disease (27 pts > 12 months (m) disease free interval) and 15 pts (21%) were stage IVb (90% visceral involvement). Moore risk distribution: 7/44/21 pts were high/medium/low risk, respectively. Eleven pts (15%) received BEV + CT; 57 pts (79%) platinum-based-CT (PCT) (54% Cisplatin; 26% Carboplatin) and 4 (6%) non-PCT. After a median follow-up of 33 m, ORR 51%, median OS 13 m (9.5-NA) and median PFS 6 m (4.6 -7.7) were observed for overall population. Moore criteria correlated with prognosis (high-risk pts had significantly worse OS (HR = 0.04, $p<0.001$). No differences in ORR, PFS or OS were detected between BEV and non-BEV group ($p > 0.2$ all comparisons). Higher ORR was observed among low and intermediate risk pts (51%, 67%; $p = 0.006$). CRs occurred in 13/71 (18%) evaluable pts (BEV group 2/11; non-BEV 11/60, $p = 1$). Clinic-pathologic features, including Moore criteria, did not correlate with CR in univariate analysis. Median time to CR was 3.5 m (3 –NA) and median duration of CR was 7 m (4.3–NA). Five pts (7%) had CR in the irradiated field. CR significantly impacted on PFS (9.7 m vs 4.7 m non-CR, $p = 0.002$) and OS (31 m vs 9.5 m non-CR, $p = 0.001$). Eight pts discontinued treatment due to toxicity.

Conclusions: CR is a meaningful surrogate marker for improved PFS and OS in MRCC pts treated with 1st line CT, but no predictive features have been identified in our cohort. Moore prognostic score was validated in real-word practice but its capability guiding therapy needs further evaluation.

Legal entity responsible for the study: Vall dHebron Institute of Oncology

Funding: None

Disclosure: A. Oaknin: Consulting or advisory role for PharmaMar, Clovis, Roche, AstraZeneca. All other authors have declared no conflicts of interest.

980P Factors Negatively Affecting Voluntary Cervical Cancer Screening Among Educated Indians Above Poverty Line

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Background: Cervical cancer is the second highest cause of cancer mortality in Indian women with 67,477 reported deaths in 2012 and 83,370 estimated deaths in 2020. Pap Smear, an affordable screening test, has shown to reduce mortality by 50 - 80% in various developed countries. However, low cervical cancer screening rate (3.1%) in India has resulted in about 70% of cases being diagnosed at an advanced stage (stage III or IV). The aim of this study is to understand reasons behind lack of voluntary testing among those educated Indians who are above poverty line and who are aware of cervical cancer being a preventable disease.

Methods: We designed a two-part web-based questionnaire containing 18 questions (~90% multiple choice questions). While the first part was designed to capture demographic attributes of the participants, the second part aimed to understand reasons behind low screening levels. The study was distributed between 1st of January 2017 to 30th of April 2017 through social media.

Results: We received a total of 212 responses. After excluding participants who are not currently residing in India or who did not complete the survey, we had 167 evaluable responses. Notably, about 50% (n = 84) of valid participants were aware of cervical cancer, indicating a decent level of awareness among the evaluable population. Among respondents who were aware of cervical cancer, 75% (n = 63) were aware that cervical cancer is preventable by regular screening. However, only 22% of 63 respondents (n = 14) underwent or took their family members for cervical cancer screening. Out of the 49 participants who did not get tested, despite being aware that cervical cancer is preventable, 57% (n = 28) stated time, 18% (n = 9) stated lack of access, and 4% (n = 2) mentioned affordability as a constraint. The remaining 21% gave other reasons most of which are related to the belief that they or their family members have low probability of falling victim to cervical cancer.

Conclusions: Time constraint emerged as the predominant reason for low cervical cancer screening levels among educated Indians who are above poverty line. We propose a proactive approach wherein stakeholders organise well-advertised, easily-accessible screening camps in the residential areas during weekends.

Legal entity responsible for the study: Oncofocus Solutions

Funding: Oncofocus Solutions

Disclosure: A. Shukla, R.M. Dokala, J.R. Philomen: Acts as an advisory firm offering research and consulting services and regularly interact with health care professionals to understand their evolving views. This research work has no commercial interest and is part of our social outreach initiative.

981P Reactive stroma mediates CD8+ T cell spatial distribution and function in ovarian cancer

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Background: Close proximity between cytotoxic T cells and tumor cells is key to effective immunotherapy. Ovarian cancer exhibits diverse immune phenotypes with distinct prevalence and spatial localization of CD8+ T cells. This study is aimed to characterize the molecular mechanisms orchestrating the localization and function of CD8+ T Cells in ovarian cancer.

Methods: CD8 IHC and RNAseq were performed on 277 ovarian tumor tissues from ICON7 phase 3 trial. CD8 T-cells in tumor vs. stromal area was assessed by digital pathology. A Random Forest regression model was constructed to identify molecular features associated with enumeration or spatial localization of CD8+ T cells. *In situ* validation was performed by MHCI IHC and FAP RNAish. Functional role of ovarian fibroblasts was characterized by *ex vivo* T cell function assays.

Results: We identified three main immune phenotypes, including T-cell infiltrated, T-cell excluded, and immune desert. The immune phenotypes are highly associated with prognosis and the molecular subtypes of ovarian cancer. The T-cell infiltrated phenotype is denoted by high expression of T-effector signatures and antigen presentation machinery. The T-cell excluded phenotype showed similar expression of T-effector signatures as the T-cell infiltrated phenotype, however, most of the CD8+ T-cells were excluded from the tumor bed. The T-cell excluded phenotype showed high expression of the reactive stroma signatures (i.e. FAP), and low expression of class I antigen presentation genes. Lastly, the immune desert phenotype featured low prevalence of CD8+ T-cells, and high expression of neuroendocrine and metabolic pathways. In situ analysis confirmed the two key molecular features associated with the T-cell excluded phenotype: 1) loss of the MHC I expression in the tumor compartment, and 2) high FAP expression in CAFs. Co-culturing of ovarian fibroblast cells with T-cells resulted in reduced T-cell activation and proliferation.

Conclusions: Our study uncovered key molecular mechanisms mediating the interplay between CD8+ T cell localization and function in ovarian cancer. Our findings underscore the potential of targeting reactive stroma as a novel therapeutic strategy to optimize immunotherapy for ovarian cancer patients.

Legal entity responsible for the study: Genentech

Funding: Genentech

Disclosure: All authors have declared no conflicts of interest.

982P Phase II study of the safety and efficacy of oral capecitabine in patients with platinum-pretreated advanced or recurrent cervical carcinoma

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Background: Cervical cancer is underrepresented in the gynecological clinical research. The objective of this observational study was to evaluate the activity and the safety of capecitabine in patients with platinum-pretreated recurrent cervical carcinoma.

Methods: In this phase II study we enrolled patients with advanced or recurrent cervical carcinoma pretreated with platinum-based therapy. All patients signed an informed consent and were treated at the Gynecological Units of the IRCCS National Cancer Institute of Milan (Italy). All patients received a starting dose of oral capecitabine 1250 mg/m^2 twice a day continuously from day 1 to day 14 every 21 days, dose reduction to 1000 mg/m^2 twice a day was permitted due to adverse events (AE). We used Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 to evaluate response to therapy and Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 to evaluate adverse events. We performed descriptive analysis and Kaplan Meier test using SPSS 20.0.

Results: From December 2013 to January 2017, we enrolled 20 patients with advanced or recurrence cervical carcinoma, already exposed to platinum, to received oral capecitabine. All patients receive a combination of carboplatin plus paclitaxel as first-line therapy for advanced/recurrent disease. Median age at the first capecitabine administration was 56.9 years (range from 27 to 82 years). After three cycles of oral capecitabine the clinical benefit rate (CBR) was 60.0% (5.0% of CR, 30.0% of PR and 25.0% of SD). No grade 3 or worse adverse events were reported. CBR was 88.8% in adenocarcinomas

versus 36.4% in squamous cell carcinomas (P = 0.067). The most frequent grade 1 or 2 adverse events were fatigue (50%), hand-foot syndrome (38.9%) and diarrhea (22.2%).

Conclusions: Our study suggests that oral capecitabine should be considered an active and safe treatment in patients with platinum-pretreated advanced or recurrent cervical carcinoma. A greater activity has been documented in patients with adenocarcinomas compared with squamous cell carcinomas.

Legal entity responsible for the study: Not applicable

Funding: None

Disclosure: All authors have declared no conflicts of interest.

983P Investigation of the clinicopathological features of vulva cancer: a retrospective survey of the JGOG Net Work study

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Background: Vulvar cancer is a rare malignancy in women. During the past 30 years, large surveys of vulva cancer have not been performed in Japan. We therefore conducted a multicenter study to clarify the clinicopathological features of vulva cancer in Japan (UMIN000017080).

Methods: In this multicenter retrospective cohort study, the clinical data of patients with vulva cancer were surveyed. The medical records of patients with vulvar cancer patients treated between 2001 and 2010 were retrospectively reviewed after obtaining approval from the Institutional Review Board of each institution. Survival analysis was performed using Kaplan-Meier curves. The effects of the clinical factors on OS were investigated using a Cox regression model.

Results: A total of 1082 patients treated in 108 centers were studied. The median age was 72 years (range, 20 to 96). The disease stage was stage I in 415 patients (38.3%), stage II in 249 (23%), stage III in 255 (23.6%), and stage IV in 163 (15.1%) (FIGO 2009). The diagnosis was squamous cell carcinoma in 779 patients (72%), Paget's disease in 158 (14.6%), adenocarcinoma in 63 (5.8%), and others in 82 (7.6%). Positive lymph nodes were found in 237 patients (21.9%). The median tumor diameter was 35 mm (range, 1 to 180). The 5-year overall survival was 86% in stage I, 74.7% in stage II, 48.2% in stage III, and 39.3% in stage IV ($P < 0.001$), and that according to histology was 63.9% in squamous cell carcinoma, 57.1% in adenocarcinoma, 79.7% in Paget's disease, and 85.4% in others. The hazard ratio was 0.51 in patients with a histology of Paget's disease or others (vs. squamous cell carcinoma or adenocarcinoma; P = 0.001; 95% CI, 0.35-0.75), 2.14 in patients with a number of positive lymph nodes 2 or more (vs. 0 or 1; $P < 0.001$; 95% CI, 1.50-43.05), 2.10 in patients with a tumor diameter of $\geq$ 35mm (vs. < 35mm; P = 0.001; 95% CI, 1.36-3.25).

Conclusions: Treatment outcomes in Japanese patients with vulvar cancer were similar to those reported previously. However, squamous-cell carcinoma, adenocarcinoma, positive lymph nodes, and bulky tumors were associated with poor outcomes. Multidisciplinary treatment might be required in patients with these characteristics.

Clinical trial identification: Registry Name: UMIN Clinical Trials Registry Registration Number: UMIN000017080

Legal entity responsible for the study: No

Funding: None

Disclosure: All authors have declared no conflicts of interest.

984TiP Japan CHARLOTTE: Characterizing the cross-sectional approach to ovarian cancer: Genetic testing of BRCA

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Background: Approximately 5–10% of breast and ovarian cancers are inherited, a condition known as hereditary breast and ovarian cancer (HBOC). Two genes, *BRCA1* and *BRCA2*, are associated with the majority of HBOC cases. Information on the frequency of g*BRCA1* and g*BRCA2* (g*BRCA1/2*) mutations in Japanese patients with ovarian cancer is limited. In a recent study of 95 unselected Japanese ovarian cancer patients, 12 (12.6%) had g*BRCA1/2* mutations. There is a need for further examination of the prevalence of g*BRCA1/2* mutations in a large number of Japanese patients. The Japan CHARLOTTE study is the first epidemiological survey in a large number of Japanese ovarian cancer patients. The primary objective is to examine the frequency of g*BRCA1/2* mutations among newly diagnosed ovarian cancer patients in Japan. The secondary objectives are to examine the frequency of g*BRCA1/2* mutations in subpopulations (e.g. histological subtype, family history), and to evaluate patient satisfaction with the explanation of *BRCA* genetic testing.

Trial design: Japanese women aged $\geq$20 years with newly diagnosed, histologically confirmed epithelial ovarian cancer, primary peritoneal cancer or fallopian tube cancer, who provide written consent for study participation within 60 days of diagnosis, are eligible. Patients who have an acute or chronic disease or mental illness that could affect the study results as judged by the attending physician will be excluded. The following data will be collected from the medical records: demographics, past medical history and medication use, reproductive history and menopausal status; diagnosis and treatment of the gynecological cancer including staging based on the FIGO stage; and CA-125 levels. A detailed family history of cancer will be obtained by interview at consultation and a blood sample will be taken for *BRCA* genetic testing. Pathological slides will be sent to a central laboratory to confirm the pathological diagnosis. A questionnaire will be administered to assess patient satisfaction with the explanation of *BRCA* genetic testing. It is anticipated that 600 patients will be enrolled, with the involvement of around 50 institutions.

Clinical trial identification: UMIN000025597

Legal entity responsible for the study: AstraZeneca K.K.

Funding: AstraZeneca K.K.

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985TiP IMagyn050 / GOG3015 / ENGOT-ov39: A randomized, double-blind, phase III study of atezolizumab vs placebo combined with chemotherapy + bevacizumab in stage III-IV ovarian, fallopian tube & peritoneal cancers (OC)

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Background: Despite surgical advances and initial responses to chemo, OC has the highest mortality among gynecologic cancers, underscoring the need to improve long-term outcomes over standard platinum/taxane regimens. OC is a VEGF-driven tumor, susceptible to both the anti-angiogenic and immunomodulatory activities of bev. The immune response may also be enhanced by blocking the PD-L1/PD-1 and PD-L1/B7.1 pathways with atezo (anti–PD-L1), further potentiating anti-cancer T-cell activity. Atezo has shown safe and durable clinical benefit as a mono- and combinatorial therapy in human cancers, including OC. Here we present the first study in OC assessing dual immunomodulation with bev + atezo with standard chemo.

Trial design: IMagyn050 (NCT03038100) will enroll $\approx$ 1300 newly diagnosed stage III-IV epithelial OC patients (pts) globally. Pts must have ECOG PS $\leq$ 2, evaluable tissue for PD-L1 testing (VENTANA SP142 assay) and will either have gross residual disease postoperatively (primary surgery group) or receive neoadjuvant (neo) therapy followed by surgery then adjuvant (adj) therapy (neo group). A concurrent phase (IV AUC6 carboplatin [Cb] + 175 mg/m^2 paclitaxel [pac] + 15 mg/kg bev + 1200 mg atezo/PL × 6 cycles [C]) will be followed by maintenance bev + atezo/PL on 21-d C for a total of 22 C atezo/PL (Table), with pts treated until completion of maintenance therapy, toxicity or recurrence, whichever occurs first. The neo group will undergo neo therapy followed by interval surgery between C3-4 then adj therapy followed by maintenance bev + atezo/PL. Stratification factors are stage and/or residual disease, ECOG PS, PD-L1 status and treatment approach. Co-primary endpoints PFS and OS will be assessed in all and PD-L1−positive ($\geq$ 1%) pts. Safety, efficacy, PROs and translational data will also be evaluated.

Table: 985TiP

Treatment Groups (1:1 randomization)	Concurrent	Maintenance
Primary surgery	C1: Cb + pac + atezo/PL C2-6: Cb + pac + bev + atezo/PL	C7 onward: bev + atezo/PL
Neo	C1-2 and 5-6: Cb + pac + bev + atezo/PL C3-4: Cb + pac + atezo/PL	C7 onward: bev + atezo/PL

Clinical trial identification: NCT03038100

Legal entity responsible for the study: F. Hoffman-La Roche Ltd.

Funding: F. Hoffman-La Roche Ltd.

Disclosure: K.N. Moore: Serve on advisory boards for AstraZeneca, Advaxis, Clovis, Tesaro, Immunogen, Genentech/Roche, VBL Therapeutics; Serve on steering committees for Advaxis, Clovis And Immunogen. F. Wu: Roche employee. Y.G. Lin: Genentech-Roche employee. S. Pignata: Honorarium by Roche. All other authors have declared no conflicts of interest.

986TiP A randomized, double-blind, placebo-controlled multicenter phase 3 trial of niraparib maintenance treatment in patients with advanced ovarian cancer following frontline chemotherapy

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Background: Niraparib (ZEJULA™) is a selective poly (ADP-ribose) polymerase (PARP) 1/2 inhibitor. In preclinical studies, niraparib concentrated in the tumor vs plasma, delivering ≥90% durable PARP 1/2 inhibition and a persistent antitumor effect. In the ENGOT-OV16/NOVA trial, niraparib demonstrated clinical efficacy in patients with recurrent ovarian cancer (OC) following complete response (CR) or partial response (PR) to platinum-based chemotherapy (PBC) regardless of *BRCA* mutation or homologous recombination deficiency (HRD) status.

Trial design: The primary objective of the ongoing ENGOT-OV26/PRIMA trial is efficacy (measured as progression-free survival) of niraparib vs placebo in advanced OC patients with CR or PR following frontline PBC. Secondary objectives include overall survival, patient-reported outcomes (PROs), time to first subsequent therapy, time to progression on the next anticancer therapy, and safety and tolerability of niraparib. Target enrollment is ≈330 patients with stage III or IV OC with PR or CR after PBC. Eligibility criteria include all patients with stage IV disease and patients with stage III disease who were treated with neoadjuvant chemotherapy followed by interval debulking surgery or who have either inoperable disease or visible residual disease after primary debulking surgery. Patients are stratified based on HRD status (HRD positive, including the known deleterious *BRCA* mutations g*BRCA*mut or s*BRCA*mut/HRD negative), neoadjuvant chemotherapy (yes/no), and best response to PBC (CR/PR). Patients are randomized 2:1 to oral niraparib 300 mg or matched placebo once daily in 28-day cycles. PRO data will be collected.

Clinical trial identification: NCT02655016

Legal entity responsible for the study: Tesaro, Inc.

Funding: Tesaro, Inc.

Disclosure: A. Gonzalez Martin: Consulting or Advisory Role: Roche, PharmaMar, AstraZeneca; Speakers' Bureau: Roche, PharmaMar, AstraZeneca; Travel, Accommodations, Expenses: Roche, PharmaMar, AstraZeneca. L.A. Rojas: Research funding: Pfizer. P.S. Braly: Speaker's Bureau: Clovis Oncology, Roche, Myriad Genetics; Research Funding: AstraZeneca, Tesaro, Janssen, PharmaMar. J. Barter: Speakers' Bureau: Baxter. D.M. O'Malley: Consulting or Advisory: Janssen Oncology, Eisai, AstraZeneca, Clovis Oncology, Genentech/Roche, Amgen, Tesaro, Novocure. A.M. Oza: Consulting or Advisory Role: Amgen, Verastem, Clovis Oncology, Immunovaccine; Travel, Accomodations, Expenses: AstraZeneca Honoraria: WebRx. C. Vulsteke: Consulting or Advisory Role: Novartis, LEO Pharma, Roche; Travel, Accommodations, Expenses: Novartis, Pfizer, Roche. D.M. Provencher: Consulting or Advisory Role: AstraZeneca; Speakers' Bureau: AstraZeneca. W. Graybill: Consulting or Advisory Role: Tesaro. Y. Li: Employment: Tesaro; Stock and other ownership interests: Tesaro. I.A. Malinowska: Employment: Tesaro; Stock and Other Ownership Interests: Tesaro. M.R. Mirza: Consulting or Advisory Role: Clovis Oncology, AstraZeneca, Tesaro. I. Vergote: Travel, Accomodations, Expenses: GCI Health, Roche, Oasmia Pharmaceutical AB, PharmaMar, AstraZeneca. B. Pothuri: Research funding: Tesaro, Caris Life Sciences, Celgene, Clovis Oncology. B.J. Monk: Consulting/Advisory: GSK, Merck, Tesaro, Roche/GNE, AZ, Gradalis, Advaxis, Verastem, Cerulean, Amgen, Vermillion, Immunogen, Bayer, NuCana BioMed, Insys Therapeutics, Clovis Onc, Oxigene, Pfizer; Speakers Bureau: Roche/GNE, AZ, Janssen, Myriad Genetics. All other authors have declared no conflicts of interest.

987TiP OReO/ENGOT Ov-38: A phase IIIb trial of olaparib maintenance retreatment in patients with epithelial ovarian cancer

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Background: A significant progression-free survival (PFS) improvement in all-comer patients (pts) with platinum-sensitive, relapsed (PSR), high-grade serous ovarian cancer supported the approval of olaparib (Lynparza™) capsules as maintenance monotherapy (Ledermann *et al NEJM* 2012); these results were confirmed using the new olaparib tablet formulation in pts with a germline *BRCA1/2* mutation (*BRCA*m) (Pujade-Lauraine *et al* SGO 2017). Pts with epithelial ovarian cancer (EOC) often retain platinum sensitivity despite progression on PARP inhibitor (PARPi) maintenance therapy. After relapse, it is unknown whether such pts could derive clinical benefit from olaparib retreatment. The OReO/ENGOT Ov-38 trial (NCT03106987; D0816C00014) will evaluate efficacy and safety of maintenance retreatment with olaparib tablets in all-comer pts with EOC.

Trial design: OReO/ENGOT Ov-38 is a randomized, placebo-controlled multicentre trial of olaparib maintenance retreatment in pts with non-mucinous EOC, and a complete or partial response to their most recent platinum-based chemotherapy. Eligibility requires prior receipt of maintenance PARPi therapy, or prior participation by pts in a study with a PARPi experimental arm. Randomization 2:1 to olaparib (300 mg twice daily tablets) or matching placebo will be split across two cohorts (approximately 416 pts): pts with a known *BRCA*m in cohort one; *BRCA* wild-type pts in cohort two. Pts with a known *BRCA*m (germline or somatic) must provide a tumour sample (archival or fresh) and a blood sample for post-analysis *BRCA* testing. Primary endpoint is investigator-assessed PFS (RECIST v1.1). Cohorts are independently powered at 80% to detect a PFS benefit (assuming a hazard ratio [olaparib:placebo] of 0.5 [cohort one] or 0.65 [cohort two]) at the two-sided 5% level. Table lists the secondary endpoints, including outcome measures for health-related quality of life. Enrolment began in Q2 2017.

Table: 987TiP Secondary endpoints

OS
TTP by GCIG criteria
TDT
TFST
TSST
PRO measures for HRQoL:
– Change from baseline in the TOI of the FACT-O
– Proportion of pts with an improved PRO score
– Best overall response (improved, no change, worsened, other)
– PRO deterioration-free survival
Safety

FACT-O, Functional Assessment of Cancer Therapy – Ovarian; GCIG, Gynecologic Cancer InterGroup; HRQoL, health-related quality of life; OS, overall survival; PRO, Patient Reported Outcome; TDT, time from randomization to study treatment discontinuation, or death; TFST, time from randomization to first subsequent treatment commencement, or death; TOI, Trial Outcome Index; TSST, time from randomization to second subsequent treatment commencement, or death; TTP, time to progression

Clinical trial identification: NCT03106987

Legal entity responsible for the study: AstraZeneca and ENGOT

Funding: AstraZeneca

Disclosure: E. Pujade-Lauraine: Received advisory board membership and honoraria from AstraZeneca and Pfizer, and advisory board membership, honoraria and speakers' bureau membership from Roche. N. Colombo: Received a grant from AstraZeneca, and personal fees from AstraZeneca, Roche, Pharmamar, Clovis, Pfizer and Tesaro. R. Glasspool: AstraZeneca: travel, registration, and accommodation for a non-compensated advisory board in June 2016, and for ASCO 2017. Advisory boards for Clovis and Tesaro (2016) and a speaker at a ROCHE meeting in March 2017. F. Marme: Received honoraria for Scientific advisory boards etc from: Roche, AstraZeneca, Novartis, Pfizer, PharmaMar, Eisai, Genmoic Health. M.R. Mirza: Board of Directors: Karyopharm., Metamark Genetics, Sera Prognostics Inc. Consultant/Advisory: Advaxis, AstraZeneca, Boehringer Ingelheim, Cerulean, Clovis, Genmab, Karyopharm, Novocure, Pfizer, Roche, Tesaro Study grants: AstraZeneca, Boehringer Ingelheim, Clovis, Pfizer, Roche, Tesaro. A. Redondo: AstraZeneca: Honoraria and travel expenses. C. Blakeley, A. Milner: Employed as a contractor for AstraZeneca, but does not own stock. All other authors have declared no conflicts of interest.

988TiP ARIEL4: An international, randomised phase 3 study of the PARP inhibitor rucaparib vs chemotherapy for the treatment of BRCA-mutated, relapsed, high-grade ovarian cancer

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Background: Approximately 18% of patients (pts) with high-grade epithelial ovarian cancer (OC) harbour a deleterious germline BRCA1 or BRCA2 (BRCA1/2) mutation, and ≈7% harbour a somatic BRCA1/2 mutation (Pennington et al. Clin Cancer Res. 2014;20:764-75). The poly(ADP-ribose) polymerase (PARP) inhibitor rucaparib is approved in the United States for the treatment of pts with deleterious BRCA mutation (germline and/or somatic) associated advanced OC who have been treated with ≥2 chemotherapies. Data comparing PARP inhibitors to standard of care (SOC) treatment for relapsed OC are limited. Randomised studies are needed to assess the benefit-risk profile of PARP inhibitors vs SOC as treatment for BRCA1/2-mutated, relapsed, high-grade OC.

Trial design: ARIEL4 (EudraCT 2016-000816-14; NCT02855944) is evaluating rucaparib vs SOC chemotherapy as treatment for pts (n≈345) with relapsed, high-grade OC (regardless of histology) and a deleterious germline or somatic BRCA1/2 mutation who received ≥2 prior chemotherapy regimens. Pts stratified by progression-free interval after their most recent platinum regimen will be randomised 2:1 to receive rucaparib (600 mg BID) (n≈230) or chemotherapy (n≈115). Pts with platinum-resistant (progressive disease [PD] ≥1 to < 6 mo after last platinum) or partially platinum-sensitive disease (PD ≥ 6 to < 12 mo after last platinum) will receive rucaparib or weekly paclitaxel; pts with platinum-sensitive disease (PD ≥ 12 mo after last platinum) will receive rucaparib or platinum-based therapy (single-agent or doublet, per investigator discretion). Pts receiving chemotherapy have the option to cross over to rucaparib upon radiographic disease progression. The primary endpoint is investigator-assessed progression-free survival (RECIST version 1.1). Secondary endpoints include overall survival, objective response rate, RECIST/CA-125 response, duration of response, and patient-reported outcomes. Safety will be summarised descriptively using standard adverse event reporting.

Clinical trial identification: EudraCT 2016-000816-14; NCT02855944

Legal entity responsible for the study: Clovis Oncology, Inc.

Funding: Clovis Oncology, Inc.

Disclosure: R.S. Kristeleit: Consulting or advisory role: Clovis Oncology, Roche/Genentech, Sotio, Lytix Biopharma, Medivation Travel, Accommodations, Expenses: Clovis Oncology, Basilea Honoraria: Clovis Oncology, Roche/Genentech, AstraZeneca. D. Lorusso: Consulting or Advisory Role: AstraZeneca, Clovis Oncology, Roche, PharmaMar Travel, Accommodations, Expenses: Roche, PharmaMar. A. Oaknin: Consulting or Advisory Role: PharmaMar, Clovis Oncology, Roche, AstraZeneca. C. Tankersley, L. Maloney, S. Goble, A. Dowson, H. Giordano: Employment: Clovis Oncology Stock and Other Ownership Interests: Clovis Oncology. C. Unger: Employment: Clovis Oncology Stock and Other Ownership Interests: Clovis Oncology, Sillajen. A.M. Oza: Consulting or Advisory Role: Amgen, Verastem, Clovis Oncology, Immunovaccine Travel, Accommodations, Expenses: AstraZeneca Honoraria: WebRx. All other authors have declared no conflicts of interest.

989TiP OCTOVA: A randomised phase II trial of olaparib, chemotherapy, or olaparib and cediranib in patients with BRCA-mutated platinum-resistant ovarian cancer

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Background: Women with platinum resistant ovarian cancer (OC) have limited responses to standard therapy, and clinical trials with novel agents are therefore highly justified. Olaparib is a potent PARP inhibitor that has shown enhanced activity in women with relapsed *BRCA*-mutated OC in both platinum sensitive and resistant settings. Angiogenesis inhibitors, such as the oral tyrosine kinase inhibitor cediranib, are active in OC, and have shown additive effects when combined with PARP inhibitors preclinically, as hypoxia-induced downregulation of homologous recombination repair genes, BRCA1, 2 and RAD51 enhances PARP inhibitor sensitivity. Recent phase 2 trials in relapsed platinum-sensitive OC have also shown benefit from the combination of olaparib and cediranib compared to olaparib alone. The OCTOVA trial investigates the benefit of single agent olaparib compared to olaparib and cediranib or weekly paclitaxel in women with *BRCA*-mutated platinum-resistant OC.

Trial design: Eligible patients for OCTOVA are females aged ≥16 years with a germline or somatic *BRCA1* or *2* mutation who have progressed within 6 months of previous platinum-based therapy. Patients may have received prior PARP inhibitor and antiangiogenic therapy, with at least a 6-month interval since treatment. 132 patients will be randomised, with stratification for prior PARP inhibitor exposure and prior antiangiogenic therapy, to one of three treatment arms: paclitaxel (80mg/m^2 weekly), olaparib (300mg twice daily), or cediranib (20mg once daily) and olaparib (300mg twice daily), until disease progression or unacceptable toxicity develops, and will be followed up for 18 months. Patients who progress on weekly paclitaxel will be permitted to crossover and receive single agent olaparib therapy. The primary analysis will compare the efficacy (as measured by progression-free survival) of olaparib compared to combination of olaparib and cediranib, and independently olaparib compared to paclitaxel. Secondary endpoints include safety and tolerability of the combination of olaparib and cediranib, overall survival, objective response rate, and quality of life outcomes.

Clinical trial identification: OCTO_062

Legal entity responsible for the study: University of Oxford

Funding: AstraZeneca (AZ)

Disclosure: S. Nicum: Consultant/Advisory Boards: Roche, AstraZeneca, Abbvie, Tesaro, Clovis Speaker: AstraZeneca, Roche Clinical Trials Sponsored: AstraZeneca. All other authors have declared no conflicts of interest.

990TiP A multicentre phase II study of AZD1775 plus chemotherapy in patients with platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer

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Background: Ovarian cancers have a high rate of mutation in TP53, an alteration that produces a G1/S checkpoint deficiency and increases the level of endogenous DNA

Table: 990TiP

	A	B	C	C2	D
AZD1775	175mg PO daily Days [D]1-2, 8-9, 15-16	225mg PO BID x 5 doses D1-3, 8-10, 15-17	225mg PO BID x 5 doses D1-3	225mg PO BID x 5 doses D1-3, 8-10 (+ D15-17 if tolerated)	175 or 225mg PO BID x 5 doses D1-3
Chemotherapy	gemcitabine 1000mg/m^2 IV D1, 8, 15 q28D	paclitaxel 80mg/m^2 IV D1, 8, 15 q28D	carboplatin AUC 5 IV D1 q21D	carboplatin AUC 5 IV D1 q21D	pegylated liposomal doxorubicin [PLD] 40mg/m^2 IV D1 q28D

Key eligibility criteria include platinum resistant OC or fallopian tube/primary peritoneal cancer (recurrence <6 months; primary refractory excluded); measurable disease per RECIST v1.1; ≤2 prior lines of therapy; ECOG PS 0-1; and *TP53*m. Approximately 97 pts will be enrolled at 26 global sites from 28 January 2015 with expected study completion in Q2 2018. Pts are restaged every 2 cycles and can continue treatment until progressive disease or unacceptable toxicity. Arms A and D enrolled 9 and 12 pts, respectively. Enrolment in Arm B was initially 8 pts and is now expanded by another 30 pts following emerging data on clinical activity. In Arm C, 6 initial pts were enrolled followed by another 17 pts; a further 12 pts will be enrolled to explore an alternative AZD1775 dosing regimen (see Arm C2 above).

damage. This can lead to a dependency on WEE1, a multifunctional protein that can induce the G2/M checkpoint, promoting the repair of DNA damage before proceeding through mitosis and cell division. AZD1775 is a highly selective small-molecule inhibitor of WEE1 that showed promising antitumor activity in TP53m refractory/resistant ovarian cancer (OC) when combined with carboplatin (Leijen et al, JCO 2016). This Phase II study (GYN 49; D6010C00004; NCT02272790) is being conducted to further explore the safety, tolerability, and preliminary efficacy of AZD1775 when combined with 4 different chemotherapy regimens in patients (pts) with platinum resistant OC and fallopian and peritoneal cancers.

Trial design: This is an open-label four-arm study, with a primary endpoint of objective response rate. Study arms are:

Clinical trial identification: D6010C00004; NCT02272790

Legal entity responsible for the study: Sarah Cannon

Funding: AstraZeneca

Disclosure: K.N. Moore: Advisory roles with several pharmaceutical companies: Clovis, Amgen, AstraZeneca, Immunogen, Genentech/Roche, Merrimack, VSL. S. Ghamande: National PI for a phase 1 dose escalation trial with a HPV Listeria vaccine for cervix cancer sponsored by Advaxis. P.A. Konstantinopoulos: Advisor for Vertex and Merck. D. Spitz: Own stock in Gilead. D. Uyar: Research project funded by Merck. G. Mugundu: Employed by AstraZeneca; owns stock in AstraZeneca and Pfizer. N. Laing: Employed by AstraZeneca, own stock in AstraZeneca, intellectual property interests in AstraZeneca. All other authors have declared no conflicts of interest.

991TiP FORWARD I: A phase 3 study to evaluate the safety and efficacy of mirvetuximab soravtansine (IMGN853) versus chemotherapy in adults with folate receptor alpha (FRa)-positive, platinum-resistant epithelial ovarian cancer, primary peritoneal cancer, or primary fallopian tube cancer

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Background: Elevated FRa expression is characteristic of a number of solid tumors, including epithelial ovarian cancer (EOC), thus providing an attractive candidate for targeted therapeutic approaches. Mirvetuximab soravtansine is an antibody-drug conjugate (ADC) comprising a potent cytotoxic effector molecule, the tubulin-disrupting maytansinoid DM4, linked to a humanized anti-FRa monoclonal antibody. In a recently completed phase 1 trial in heavily pre-treated ovarian cancer patients, mirvetuximab soravtansine showed a favorable safety profile and promising single-agent clinical activity.

Trial design: FORWARD I is a randomized phase 3 study designed to evaluate the efficacy of mirvetuximab soravtansine compared to standard-of-care chemotherapy in adult patients with platinum-resistant EOC, primary peritoneal cancer, or fallopian tube cancer. Inclusion criteria include confirmation of tumor FRa positivity by immunohistochemistry (medium or high receptor expression; ≥ 50% of cells with at least moderate staining intensity) and ≤ 3 prior lines of therapy. A total of 333 patients are expected to be recruited, who will be randomized 2:1 to mirvetuximab soravtansine dosed intravenously at 6.0 mg/kg, calculated according to adjusted ideal body weight, on Day 1 of a 21-day cycle or investigators' choice chemotherapy (paclitaxel, pegylated liposomal doxorubicin, or topotecan). Progression-free survival (PFS; assessed by blinded independent central review) is the primary efficacy endpoint; secondary endpoints include objective response rate, quality of life, overall survival, safety and tolerability, and duration of response. The first patient enrolled in January 2017.

Clinical trial identification: NCT02631876

Legal entity responsible for the study: ImmunoGen, Inc.

Funding: ImmunoGen, Inc

Disclosure: K.N. Moore, I. Vergote: Advisory board service for ImmunoGen, Inc. K. Malek: Employed by ImmunoGen, Inc. M.J. Birrer: Advisory board service for ImmunoGen, Inc. All other authors have declared no conflicts of interest.

992TiP N-DUR: Matched pair pharmacodynamics study of neoadjuvant durvalumab in combination with chemotherapy in frontline ovarian cancer

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Background: Although upfront treatment for ovarian cancer (OC) achieves complete remission in over 70% of women, the majority of patients (pts, 80%) relapse and die from disease. Thus, there is great interest in improving standard of care and exploring maintenance strategies. Immune evasion and suppression is a central feature of the OC microenvironment. Immune abrogation has also been linked to primary and adaptive chemoresistance and angiogenesis. Prolongation of immunocompetence represents a promising intervention to achieve lasting tumor suppression promoting survival. Further, chemotherapy may increase immunogenicity by releasing tumor-specific antigens providing an environment for long-term tumor control. Governance of T cell regulation with immune therapy has been explored in advanced solid tumors. Clinical experience with agents targeting PD-1/PD-L1 in OC is limited but responses have been observed. Durvalumab is a novel PD-L1 inhibitor with activity across a number of different solid tumors in in vitro and in vivo models. As yet, it is unknown which pts stand to benefit the most from this agent.

Trial design: A total of 30 evaluable pts with untreated, advanced stage OC undergoing neoadjuvant chemotherapy will be treated with paclitaxel, carboplatin and durvalumab, followed by durvalumab maintenance. Pretreatment biopsies will be obtained at laparoscopy or by interventional radiology from up to 4 sites. Interval tumor reductive surgery (TRS) will be performed after 3 cycles. Matched biopsies will be obtained at TRS. The study incorporates a phase I safety lead in (n = 6) to ensure the combination has acceptable toxicity and pts undergo TRS in a timely fashion. Dose-limiting toxicities (DLTs) will be assessed. This will be followed by open enrollment on the phase II portion. The primary objective is to explore basal levels and effects of durvalumab in combination with chemotherapy on molecular markers in immune-related pathways and lymphoid populations including DNA copy number, mutation, RNA/protein expression, PD-L1 expression and T-cell infiltration, before and after treatment. Secondary objectives are progression free survival, overall survival, and patient reported outcomes.

Clinical trial identification: NCT02726997 March 24, 2016

Legal entity responsible for the study: The University of Texas MD Anderson Cancer Center

Funding: AstraZeneca, Ovarian Cancer Moonshot, Sabin Family Foundation

Disclosure: S. Westin: Research Support: AstraZeneca, Novartis, Critical Outcomes Technologies, Inc Advisory Board/Consulting: AstraZeneca, Clovis, Roche/Genentech, Ovation, Medivation, Vermillion, Casdin Capital. A. Jazaeri: Research Support: AstraZeneca, Lion Biotech, Pfizer Advisory Board/Consulting: EMD-Serono, Genentech. M. Frumovitz: Research Support: Novadaq; Consulting: Novadaq. P. Soliman: Research support: Novartis. G. Mills: Research Support: Abbvie, Adelson Medical Research Foundation, AstraZeneca, Nanostring, Pfizer, Tesaro Consulting: AstraZeneca, Medimmune, Pfizer Licensed technology HRD assay to Myriad Genetics. A. Vergara-Silva: Employee of AstraZeneca/MedImmune. R. Coleman: Research Support: AstraZeneca, Clovis, Janssen, Abbvie, Merck, Roche/Genentech, Millennium; Advisory Board/Consulting: AstraZeneca, Clovis, Janssen, Abbvie, Merck, Roche/Genentech, Millennium, Tesaro, Novartis, Pfizer, Bayer, Array, Millennium. All other authors have declared no conflicts of interest.

993TiP Comparing doses and fractionation regimens for high dose rate brachytherapy in locally advanced cervical carcinoma: A randomized controlled trial

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Background: Cervical cancer is among the most common gynecologic malignancies encountered in Low and Middle Income Countries. Tanzania, and the whole East African region where it belongs, has cervical cancer as the first malignancy in women, in both incidence and mortality. Despite the advances in management of cervical carcinoma, most of the Low-Income Countries lag in terms of treatment planning and delivery, considering the loads of patients that consult on a regular basis. Locally advanced cervical cancer status, as defined by the International Federation of Gynecology and Obstetrics confers to the patient a high recurrence and low survival rate risks altogether. Survival rates have been shown to have a decreasing tendency as the cancer stage increase. According to FIGO classification, the management of a locally advanced cervical cancer consists of a course of combined radiotherapy and chemotherapy, with a few added weeks of brachytherapy. As it has been shown before, both exposure and toxicity to any of the available treatment options could be lowered if some factors are taken into consideration. Encouraging results have been shown elsewhere. This study compares two different dose fractionations of High dose rate brachytherapy for selected cases of cervical carcinoma, and seeks to prove feasibility of both.

Trial design: The study is an open-label, single institution, non-inferiority, phase 3 randomized controlled trial. Patients will be assigned (1:1), with a consecutive recruitment according to set randomization criteria, to receive two brachytherapy insertions of 8.5 Grays, one week apart (intervention group – A) or three brachytherapy insertions of 6.7 Grays, one week apart (control group – B). Patients will be enrolled then randomized to either group after satisfactory completion of a 5 week-course of both external beam radiotherapy, total dose of 50 Grays, on a 2 Gray daily in 25 fractions, combined with a weekly single agent cisplatin for a dose of 40 mg/m^2. The study will have a recruitment phase spanning between April to June 2017 and a follow up phase from May 2017 to May 2018.

Legal entity responsible for the study: Muhimbili University of Health and Allied Sciences

Funding: None

Disclosure: All authors have declared no conflicts of interest.

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

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HAEMATOLOGICAL MALIGNANCIES

994O Equivalent efficacy of a biosimilar rituximab and reference rituximab in previously untreated advanced follicular lymphoma: Extended results of ASSIST-FL, a confirmatory phase III study

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Background: GP2013, a rituximab biosimilar, has been developed according to biosimilar development guidelines, with clinical trials in rheumatoid arthritis and follicular lymphoma (FL).

Methods: This confirmatory phase III, double-blind, randomized, controlled trial compared efficacy, safety, pharmacokinetics (PK) and pharmacodynamics (PD) of GP2013-CVP versus rituximab-CVP (R-CVP) in previously untreated, advanced-stage FL. The primary endpoint was equivalence in overall response rate (ORR), defined by 95% confidence interval [CI] with a margin of ± 12%. Secondary, non-powered endpoints comprised progression-free and overall survival, PK, PD, and safety. Patients were stratified by region and FLIPI risk score and randomized (1:1) to 8 cycles of GP2013-CVP (n = 314) or R-CVP (n = 315), followed by monotherapy maintenance for up to 2 years in responders (ClinicalTrials.gov identifier: NCT01419665).

Results: The primary endpoint, equivalence of ORR between treatments, was met (GP2013-CVP: 87.1%; R-CVP: 87.5%; difference [95%CI] –0.40% [–5.94%, 5.14%]). Subgroup analyses suggested that ORR was similar between GP2013-CVP and R-CVP regardless of age (<, ≥60 years), gender, race, geographic region or bulky disease. Subgroup analyses reported numerical treatment differences (95%CI) of –8.41 (–17.09, 0.28) and 5.74 (–1.70, 13.17) for patients with FLIPI score of 0–2 and 3–5, respectively. Safety data from an interim analysis with an additional year of follow up showed that the pattern and rates of AEs (combination period: GP2013-CVP, 92.9%; R-CVP, 91.4%; maintenance period: GP2013, 72.0%; R, 69.4%) and SAEs (combination period: GP2013-CVP, 22.8%; R-CVP, 20.0%; maintenance period: GP2013 7.9%; R, 7.1%) are similar between treatments.

Conclusions: The study demonstrated equivalence in ORR between the biosimilar GP2013 and reference rituximab in patients with previously untreated, advanced FL. Similarity in ORR was observed across subgroups and safety profiles were also comparable. Based on the totality of evidence, GP2013 was approved by the EMA and represents an important option for patients that need rituximab and to help sustain the cost of cancer care.

Clinical trial identification: NCT01419665

Legal entity responsible for the study: Hexal AG, a Sandoz company, part of the Novartis group

Funding: Hexal AG

Disclosure: W. Jurczak: Received research funding and lecture honoraria from Sandoz. P. Zhu, S. Alexandrova: Employee of Sandoz Inc. Princeton, NJ, USA. A. Zubel, O. Harlin, J. Amersdorffer: Employee of Hexal AG, Holzkirchen, Germany. All other authors have declared no conflicts of interest.

995O Interim results from a phase 1 first-in-human study of flotetuzumab, a CD123 x CD3 bispecific DART molecule, in AML/MDS

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Background: Acute myeloid leukemia (AML) CD34+, CD38- cells highly express CD123, associated with high-risk disease and disease progression. CD123 expression on normal HSC is negligible, enabling a promising strategy of preferential ablation with a CD123-targeted approach. Flotetuzumab (MGD006/S80880), a novel CD123 x CD3 bispecific DART protein, is designed to target CD123+ cells for elimination by T cells.

Methods: The Ph 1 dose-escalation study will define the safety profile, maximum tolerated dose and schedule (MTDS), and preliminary anti-leukemic activity of flotetuzumab. Relapsed/refractory (R/R) AML or intermediate-2/high-risk MDS will be treated with 28 day cycles of continuous infusion at doses from 3 to 1000 ng/kg/day. During C1W1, patients receive a lead-in dose (LID) of 30 ng/kg/day for 3 days followed by 100 ng/kg/day for 4 days. During C1W2-4, patients receive the cohort target dose (300-1000ng/kg/day) on either a 4-day on/3-day off or a continuous 7-day on weekly schedule. At Cycle 2 and beyond, patients are treated on a 4-day on/3-day off schedule at the cohort target dose for a maximum of 12 cycles, 2 cycles after a CR, DLT or DP. Cohort expansion will enroll 24 AML and 24 MDS patients at the MTDS. Disease status is assessed by IWG criteria.

Results: Patients with R/R AML/MDS (35/3) have been treated with flotetuzumab, up to a dose of 500ng/kg/day. Flotetuzumab has demonstrated acceptable tolerability to date, with no MTDS yet defined for either schedule. The most common drug-related adverse event was infusion-related reaction/cytokine-release syndrome (29/38, 76% any grade; 3/38, 8% G3). Drug-related adverse events ≥G3 were observed in 14/38 (36%) of patients overall. A LID strategy and early use of tocilizumab ameliorated this toxicity and limits corticosteroid use. At 500ng/kg/day, anti-leukemic activity has been observed in 4/8 patients treated, including CRi (n = 2), morphologic leukemia free state (n = 1) and bone marrow blast reduction >50% (n = 1).

Conclusions: To date flotetuzumab has an acceptable safety profile and demonstrated early evidence of anti-leukemic activity.

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996O Risk of developing acute myeloid leukemia (AML) in well-differentiated thyroid cancer (WDTC) patients treated with radioactive iodine (RAI): a population-based study

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Background: Risks of leukemias increase after radiation treatment, including RAI, which is frequently used to treat WDTC. However, the risk of AML following RAI treatment in WDTC survivors has not been characterized.

Methods: In a population-based study, we queried all 18 Surveillance Epidemiology and End Results registries for WDTC cases treated with surgery or surgery followed by RAI. We assessed the risk dynamics of developing AML in WDTC patients and its association with RAI. We also studied the clinical outcome of AML that occurred after WDTC diagnoses in case-control studies.

Results: Of 148,215 WDTC patients identified between 1973-2014, 55% received surgery alone and 45% received surgery and RAI. After a median 4.3 person years of follow up (IQR, 1.9-7.4), 44 patients developed AML after surgery alone for WDTC and 56 patients developed AML after surgery and RAI. Compared to the background rates in the general population, patients treated with surgery and RAI had an increased risk of developing AML that peaked within the first three years after RAI treatment (RR: 5.6, 95% CI: 3.8-8.1, $P < 0.0001$). After correction for sex and WDTC tumor size in a multivariate analysis, patient age (HR: 1.03, 95% CI: 1.02-1.05, $P < 0.001$), WDTC tumor stage (HR: 1.36, 95% CI: 1.04-1.79, $P = 0.03$) and RAI treatment for WDTC as compared with thyroidectomy alone (HR: 1.38, 95% CI: 1.09-1.75, $P = 0.007$) were independent prognostic factors for AML development. WDTC patients that developed AML after surgery and RAI had a truncated survival as compared with matched WDTC control patients that did not develop AML (median OS: 7.5 years *vs.* 24.4 years, $P < 0.0001$). Finally, patients that were diagnosed with AML after RAI treatment for WDTC had a worse prognosis than patients with AML that occurred spontaneously (median OS: 1.2 years *vs.* 3.5 years, $P = 0.004$).

Conclusions: RAI treatment is associated with an increased risk of developing AML in WDTC survivors. RAI-related AML has a poor survival, similarly to t-AML that arises after radiotherapy or chemotherapy. Considering young patient ages at WDTC diagnosis and high survival rates, the rates of AML in WDTC survivors are likely to continue to rise.

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997PD Split dosing of daratumumab (D) in a phase 1b study of D plus carfilzomib (K)-based regimens in patients (pts) with multiple myeloma (MM)

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Background: D, a human CD38 IgGκ mAb, induces deep, durable responses in pts with relapsed/refractory MM, as monotherapy and combined with other regimens. Infusion-related reactions (IRRs) occur in ~50% of D-treated pts, are generally mild to moderate, and usually occur during the 1st infusion. The median duration of the 1st infusion is ~7 hours. To determine if splitting the first dose would reduce IRRs and infusion times, split-dose D was evaluated in two K-based regimens (MMY1001: NCT01998971).

Methods: Pts received D plus K and dexamethasone (d; DKd) or DKd and lenalidomide (R; DKRd). Pts in the DKd arm had 1-3 prior therapies; pts in the DKRd arm were newly diagnosed. 28-day cycles comprised K 20 mg/m^2 intravenously (IV) over 30 minutes on Cycle 1 Day 1 (C1D1) and 70 mg/m^2 over 30 minutes weekly, thereafter; and weekly d 40 mg (20 mg if > 75 years). In the DKRd arm, R 25 mg was given orally on Days 1-21. Pts received IV D as a single or split dose (**Table**). If C1D1 and C1D2 D infusions were not well-tolerated, C1D8 was given in 1000 mL. Pts received treatment until progression (DKd) or for ≤13 cycles (DKRd). To mitigate IRRs, d (20 mg) was given ≤3 hours before dosing on C1D1 and C1D2, and ≤3 hours before and the day after subsequent infusions. Paracetamol and diphenhydramine were given ≤3 hours before infusion. Montelukast was given prior to first D dose (optional thereafter).

Results: Thirty-two pts received split-dose D. Median age (range) was 61 (34-76) years. Median number of D cycles received was 12 (1-14). Median first infusion time was 4.2 (4.0-10.3) hours. Among pts who received split-dose D, 9 (28%) pts had an IRR. Five (16%) and 4 (13%) pts had grade 1 and grade 2 IRRs, respectively. No grade 3/4 IRRs occurred. IRRs reported in ≥ 2 pts were cough, throat irritation, nausea, and headache (2 pts [6%] each). Data will be updated.

Conclusions: A split first dose of D was associated with shorter infusion times and reduced incidence and lower grade of IRRs.

Table: 997PD

	Split dose C1D1 and C1D2 (8 mg/kg)	Second dose C1D8 (16 mg/kg)	Subsequent doses (16 mg/kg)
Initial rate, mL/hour	50	50	100
Rate increment increase per hour, mL/hour	50	50	50
Maximum rate, mL/hour	200	200	200
Total infusion, mL	500	500	500

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998PD Management of infusion-related reactions (IRRs) in patients (pts) receiving daratumumab plus standard of care for the treatment of multiple myeloma (MM) in the phase 3 studies CASTOR and POLLUX

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Background: Daratumumab (D), a CD38-targeted monoclonal antibody, reduced the risk of MM progression or death by > 60% when combined with standard-of-care regimens in the phase 3 studies CASTOR (bortezomib [V] and dexamethasone [d] vs DVd; NCT02136134) and POLLUX (lenalidomide [R] and d vs DRd; NCT02076009). This analysis evaluated the management of D-related IRRs in the DVd and DRd arms of CASTOR and POLLUX.

Methods: Pts had MM and had received ≥1 line of therapy. In CASTOR, pts were given 8 21-day cycles of Vd (V 1.3 mg/m^2 subcutaneously on Days 1, 4, 8, and 11; d 20 mg per os [PO]/intravenously [IV] on Days 1-2, 4-5, 8-9, and 11-12) ± D (16 mg/kg IV, weekly [QW] for Cycles 1-3, every 3 weeks [Q3W] for Cycles 4-8, then every 4 weeks [Q4W] thereafter). In POLLUX, pts were given 28-day cycles of Rd (R 25 mg PO on Days 1-21; d 40 mg QW) ± D (16 mg/kg IV QW for Cycles 1-2, every 2 weeks for Cycles 3-6, then Q4W thereafter). In addition, pre-infusion medication consisted of 20 mg d (or equivalent) IV/PO, 650-1000 mg paracetamol, and 25-50 mg diphenhydramine (or equivalent). Pts with high-risk respiratory complications received diphenhydramine on Days 1 and 2, a short-acting β2 adrenergic receptor agonist and control medications for lung disease after D infusion.

Results: All pts receiving D were given pre-infusion medication. In CASTOR and POLLUX, 31 (13%) and 21 pts (7%) received post-infusion medications, respectively. In both trials, the median duration of D infusion was ~7.0, 4.3, and ~3.4 hours for the first, second, and subsequent infusions, respectively. IRRs occurred in 45% and 48% of pts and 98% and 96% of IRRs occurred during the first infusion in CASTOR and POLLUX, respectively. Most IRRs were grade 1/2 and no grade ≥4 IRRs were reported.

The median time to onset of IRRs after starting the first D infusion was 84 minutes in CASTOR and 90 minutes in POLLUX. In CASTOR, 2 pts discontinued treatment due to IRRs; in POLLUX, 1 pt discontinued D due to a grade 3 IRR, but continued Rd.

Conclusions: Most D-related IRRs occurred during the first infusion and were grade 1/2. D-related IRRs were easily managed with pre- and post-infusion medications.

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999PD Comparison of efficacy of new therapies between younger and older patients with relapsed and refractory multiple myeloma: A meta-analysis

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Background: Multiple myeloma is a disease of age. With all of the new myeloma drugs being developed, there are number of treatment options for relapsed and refractory multiple myeloma (RRMM). However, in our knowledge, few data are available in patients older than 65 or 75 years. We performed a meta-analysis to compare the efficacy of new drugs to treat RRMM between younger and older patients.

Methods: PubMed and the Cochrane databases were searched up to April 2016. We included phases III randomized controlled trials (RCTs) of monoclonal antibodies (mAbs) targeting CD38 or SLAMF7 (daratumumab, elotuzumab), second generation proteasome inhibitors (carfilzomib, ixazomib) and histone deacetylase (HDAC) inhibitors (vorinostat, panobinostat) reporting subgroups comparison of progression-free survival (PFS) based of aged cut-offs. The summary hazard ratio (HR) and 95% confidential interval (CI) were calculated.

Results: A total of 5241 patients from eight RCTs of RRMM new therapies were included (CASTOR, POLLUX, ELOQUENT-2, ASPIRE, ENDEAVOR, TOURMALINE-MM1, PANORAMA-1 and VANTAGE-088). When patients are dichotomized into younger and older groups with an age cut-off of 65-75 years, RRMM new therapies improved PFS in both younger (HR, 0.62; 95% CI, 0.56–0.70) and older (HR, 0.67; 95% CI, 0.60–0.74) groups. An improvement in PFS with mAbs was observed in younger (HR, 0.57; 95% CI, 0.46–0.72) and older (HR, 0.52; 95% CI, 0.42–0.64) patients. An improvement in PFS with HDAC inhibitors was also observed in both younger (HR, 0.67; 95% CI, 0.56–0.80) and older (HR, 0.78; 95% CI, 0.63–0.97) as well as with second generation proteasome inhibitors (HR, 0.61; 95% CI, 0.52–0.73 and HR, 0.70; 95% CI, 0.60–0.81 respectively).

Conclusions: A benefit in PFS with new therapies was significant in both younger and older patients with relapsed and refractory multiple myeloma with a cut-off age of 65–75 years.

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1000PD Copanlisib treatment in patients with relapsed or refractory indolent B-cell lymphoma: Subgroup analyses from the CHRONOS-1 study

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Background: Copanlisib, a pan-class I phosphatidylinositol 3-kinase (PI3K) inhibitor with predominant activity against PI3K-α and PI3K-δ isoforms, has recently been shown to achieve a 59% objective tumor response rate (ORR) in a phase II study in patients with relapsed or refractory (r/r) indolent B-cell lymphoma. We report here the results of subgroup analyses conducted based on demographic and baseline disease characteristics.

Methods: Patients with indolent B-cell non-Hodgkin lymphoma (4 subtypes: follicular [FL], marginal zone [MZL], small lymphocytic [SLL] and lymphoplasmacytoid/Waldenström macroglobulinemia [LPL-WM]) and r/r to ≥ 2 prior lines of treatment were eligible. Previous treatment had to include rituximab and an alkylating agent. Copanlisib (60 mg, I.V.) was administered intermittently on days 1, 8 and 15 of a 28-day cycle. The primary efficacy endpoint was ORR as assessed per independent radiologic review (Cheson et al. 2007).

Results: The full analysis set comprised 142 patients, of which 141 patients had indolent lymphoma (FL/MZL/SLL/LPL-WM: 104/23/8/6). ORR per histological subgroup was 58.7%/69.6%/75.0%/16.7%, respectively. ORR based on demographics were generally consistent across categories. Likewise, there were no major differences in ORR between any of the baseline disease characteristics and prior therapy subgroups with regards to ECOG PS (0 [58.8%] vs. ≥ 1 [59.7%]), longest diameter of baseline lesion (< 7cm [59.8%] vs. ≥ 7cm [59.1%]), received prior bendamustine (yes [62.7%] vs. no [56.6%]), number of prior therapies (< 4 [59.8%] vs. ≥ 4 [57.5%]), or refractoriness to last regimen (yes [60.5%] vs. no [57.1%]). Median duration of response (DOR) by tumor histology for the subgroups with ≥ 10 responders was 370 days (range 33-687) for FL patients and had not yet been reached for MZL patients (2 of 16 responders having progressed).

Conclusions: Objective response rates were consistently high in patients with r/r indolent B-cell lymphoma treated with copanlisib with the exception of LPL-WM patients. There were no major differences in the ORR between any of the baseline disease characteristics and prior therapy subgroups, confirming the robustness of the primary efficacy endpoint.

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1001PD Tumor gene expression signatures of BCR/PI3K dependence in association with copanlisib monotherapy activity in heavily pretreated patients with indolent NHL and follicular lymphoma

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Background: Copanlisib, a novel class I PI3K inhibitor with predominant activity against α and δ isoforms, has shown robust single agent anti-tumor activity in a phase 2 study in heavily pretreated patients with indolent NHL (iNHL) and follicular lymphoma (FL) (NCT01660451; Part B), with response rates of 59.6% and 58.7%, respectively. Baseline tumor gene expression profiling (GEP) was performed to confirm if gene signatures identified in patients with indolent or aggressive NHL (NCT01660451; Part A) are molecular determinants for copanlisib antitumor activity in Part B.

Methods: Signaling pathway gene sets (n = 33) were ranked by enrichment analysis (GSEA) for association with objective response based on normalized enrichment score (NES) and false discovery rate (FDR) q values. The association of weighted gene-expression score (WGS, reflecting the overall expression level for each gene set) with response was analyzed by logistic regression.

Results: Seventy-one patients with iNHL, including 54 FL, had both response data and evaluable gene expression data. All 5 gene sets reflecting upregulated PI3K/BCR signaling were top-ranked for association with higher response rates in iNHL (GSEA NES $\geq$ 1.93, FDR q $<$ 0.01; WGS AUC $\geq$0.65, nominal p $\leq$ 0.04) and FL (GSEA NES $\geq$1.50, FDR q $\leq$ 0.01; WGS AUC $\geq$0.60, nominal p $\leq$ 0.23). Among patients with objective responses, 66% (33/47) of iNHLs and 71% (24/36) of FLs had high PI3K/BCR gene signature expression levels; for patients with CR, 86% (6/7) iNHL and 83% (5/6) FL had high levels. Further, 4 gene sets enriched with T-cell signatures were associated positively with copanlisib response (NES $\geq$1.48, FDR q $\leq$ 0.08). In contrast, up-regulation of macrophage/stromal gene sets was potentially associated with a lower likelihood of response to copanlisib treatment in FL (NES $\leq$ -1.21, q $\leq$ 0.21).

Conclusions: Tumor gene expression profiling demonstrates that up-regulation of the BCR/PI3K pathway is frequent and dominant in iNHL and FL, and is associated with the high and durable copanlisib responses. These findings are consistent with copanlisib's mode of action and strongly support the rationale for treatment of iNHL and FL patients with copanlisib.

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1002PD Standardized mortality ratios and event-free survival as new prediction tools of early increase in mortality in follicular lymphoma

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Background: There are few studies that analyze follicular lymphoma (FL) mortality compared to the general population of the same -sex and age group. Given the recent clinical relevance of the predictive event-free survival (EFS) indexes EFS12 and EFS24, we obtained them in our study cohort in order to estimate their association with overall survival (OS).

Methods: Patients diagnosed with FL were prospectively enrolled from 1980 to 2013. Standardized mortality ratios (SMR) were obtained using yearly sex and age specific mortality rates in Spain, and OS was compared with age- and sex-matched general population data. EFS were defined as the time from diagnosis until relapse or progression, unplanned retreatment of lymphoma after initial management, or death due to any cause. EFS12 and 24 were defined as EFS status at 12 or 24 months from diagnosis, respectively. The crude probability of death was estimated by using the Kaplan–Meier method, and differences between patient groups were assessed by the log-rank test. In order to investigate the specific contribution of age, sex, period of diagnosis, treatment and FLIPI score, a multivariable Cox proportional hazards model was adjusted, all statistical tests were two-sided, and a p-value $<$0.05 was considered statistically significant.

Results: A total of 1074 patients with newly diagnosed FL were enrolled. The median OS was 231 months (CI 95% 195-267). EFS at 12 and 24 months was associated with increased probability of early death, with an SMR of 10.27 (95% CI: 8.26-12.77). The prognostic value of traditional scales such as FLIPI is maintained in our study, with a hazard ratio of 2.7 (95% CI: 1.9- 4.0) for a score of 2-5. Of note, no significant difference in mortality was observed between FL patients at 10 years since diagnosis compared to the general population (SMR of 1.02; 95% CI 0.57, 1.85).

Conclusions: EFS12 and 24 predicted an early increase in mortality. The long-term SMR, over 10 years of follow-up, shows that patients with FL have a similar risk of dying than the general population of the same sex and age.

Legal entity responsible for the study: GOTEL (Spanish Lymphoma Oncology Group)

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1003PD A multicentre phase II trial addressing lenalidomide (LEN) maintenance in patients with relapsed diffuse large b-cell lymphoma (rDLBCL) who are not eligible for autologous stem cell transplantation (ASCT)

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Background: Single-drug maintenance after salvage therapy could prolong survival of pts with rDLBCL not eligible to ASCT. LEN could be an excellent candidate as it is an oral agent, active against DLBCL, with excellent safety profile. Herein, we report results of a multicentre phase II trial addressing LEN maintenance (mLEN) in pts with chemosensitive rDLBCL.

Methods: HIV-negative pts with DLBCL relapsed after R-CHOP or similar and responsive to salvage therapy were registered and treated with LEN 25 mg/day for 21 days out of 28 until lymphoma failure or unacceptable toxicity. Primary endpoint was the 1-year PFS. Estimated sample size (Simon's two-stage optimal design; type I error 5%, power 80%, P0 30%, P1 50%) was 47 pts; mLEN would be considered effective if $\geq$ 19 pts will be progression-free survivors at 1 year. The prognostic role of cell of origin, assessed by NanoString and Hans algorithm, was investigated.

Results: 46 of 48 enrolled pts were assessable (median age 72 years; 34-86); 26 pts started mLEN in CR and 20 in PR after salvage therapy. 639 LEN courses were delivered, with an average of 14 courses/pt (3-53). LEN was well tolerated: with the exception of neutropenia, grade 3-4 toxicities were uncommon ($\leq$3% of courses). LEN dose reduction was indicated in 25 pts. Three pts died of toxicity: intestinal infarction, meningitis, unknown cause; 2 pts developed a second cancer. The pre-determined efficacy threshold (n $\geq$ 19) was largely achieved: 32 pts were progression free at 1 year from registration. At a median follow-up of 38 (14-95) months, 23 events occurred: PD in 19 pts, death of toxicity in 3, death while off therapy in 1, with a 1-yr PFS of 70% (95%CI=59-81). The benefit of mLEN was observed both in pts with *de novo* or transformed DLBCL, and both in GCB- or nonGCB-DLBCL. 29 (63%) pts are alive, with a 3-yr OS of 64%.

Conclusions: With the limitations of a non-randomized design, this trial soundly promotes the use of mLEN in pts with chemosensitive rDLBCL not eligible for ASCT or experiencing relapse after ASCT. These results warrant further investigation of immunomodulatory drugs as maintenance in these high-risk pts.

Clinical trial identification: NCT00799513

Legal entity responsible for the study: IRCCS San Raffaele

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1004PD Follicular lymphoma: clinical and mollecular characteristics of histologic transformation

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Background: Follicular lymphoma (FL) is the second most common type of non-Hodgkin lymphoma (NHL). Histological transformation (HT) refers to the evolution

of a clinically indolent NHL to an aggressive one. The rates of HT in published series range from 10% to 60%. There are no specific clinical characteristics that can predict transformation. Some molecular parameters associated with transformation are: p53 expression, expression of c-MYC, BCL-6 mutations. This suggests that multiple alternative mechanisms are likely to be involved in the pathogenesis of HT.

Methods: We report a prospective, multicenter (39 Spanish member institutions of Grupo Oncológico para Tratamiento de Linfomas-GOTEL-), observational study designed to collect data on disease presentation, treatment and clinical outcomes of HT. Inclusion criteria for this analysis were initial diagnosis of grade 1-3a FL and enrolment from 1990 to 2016. HT was defined as refractory/recurrent disease with clinical or pathologic diagnosis. Whole exome sequencing of the HT samples has been performed and compared with samples from patients with LF without transformation.

Results: Of the 975 evaluable patients, 64 had HT. Characteristics associated with an increased risk of HT were: the presence of B symptoms ($p = 0.001$), increased LDH ($p = 0.02$), high Follicular Lymphoma International Prognostic Index (FLIPI) ($p = 0.01$) and poor perfomance status ($p = 0.01$). In this group of patients, the cumulative incidence rate of HT at 5 years was 7.3%; the rate of HT remained constant, reaching a plateau after 14 years. Expectant management also predicted for a higher risk of HT ($p = 0.0001$). The median survival from transformation was 5 years. Regarding molecular characteristics, we found that all patients with HT had more than 4 mutations at diagnosis of FL in a group of 14 genes that are frequently mutated in patients with HT: CSMD3, DTX1, FOXO1, LRP1B, NOTCH2, PIM1, POU2F2, ATM, BCL7A, HIST1H1E, IRF8, PCLO, EZH2 and TNFAIP3.

Conclusions: There are clinical (increased LDH, B symptoms, high FLIPI, poor performance status) and molecular factors (more than 4 mutations in specific genes) at diagnosis correlate with an increased risk of HT. These predictors of HT could help to develop targeted therapies to prevent HT in high risk patients or improve current salvage approaches.

Legal entity responsible for the study: GOTEL (Grupo Oncológico para el Tratamiento y Estudio de Linfomas)

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1005PD Prognostic nomogram for overall survival in previously untreated patients with diffuse large B-cell lymphoma

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Background: The purpose of this study was to develop a newly accepted prognostic nomogram to estimate overall survival (OS) in patients with diffuse large B-cell lymphoma (DLBCL) and assess its incremental value to the traditional International Prognostic Index (IPI) and NCCN-IPI for individual OS estimation.

Methods: The clinical data from 1,118 patients with DLBCL treated at Cancer Hospital Chinese Academy of Medical Sciences between 2006 and 2012 were reviewed. A nomogram was developed that predicted OS based on the Cox proportional hazards model. To contrast the utility of the nomogram against the widely used IPI and NCCN-IPI, we used the concordance index (C-index) and a calibration curve to determine its predictive and discriminatory capacity.

Results: The 5-year OS rate was 64.1% for the entire group. The entire group were divided into the primary ($n = 783$) and validation ($n = 335$) cohorts. The nomogram included eight important variables based on a multivariate analysis of the primary cohort: Ann Arbor stage; age; ECOG PS; LDH; β2-MG; CD5; Bcl-6 and Ki-67 index. The calibration curve showed that the nomogram was able to predict 5-year OS accurately. The C-index of the nomogram for OS prediction was 0.77 in the primary cohort and 0.76 in the validation, which was superior to the predictive power (range, 0.71-0.74) of the IPI and NCCN-IPI in the primary and validation cohorts. To detect the accuracy of the nomogram for rituximab plus CHOP (R-CHOP) like regimen, we took subgroup analysis. The C-index of the nomogram for OS prediction was 0.78 in the R-CHOP like regimen subgroup, and 0.76 in the CHOP like regimen subgroup.

Table: 1005PD Multivariate analysis of 783 patients in the primary cohort

Covariate	level	HR	95% CI	P-value	nomogram score
Age	>60y	1.32	1.02-1.72	0.036	28
	≤60y	–	–	–	0
ECOG PS score	≥2	1.84	1.38-2.44	<.001	62
	0 or 1	–	–	–	0
LDH	Elevated	1.64	1.27-2.12	<.001	50
	Normal	–	–	–	0
Ann Arbor stage	Stage IV	2.69	1.81-3.99	<.001	100
	Stage III	1.88	1.22-2.88	0.004	64
	Stage II	1.25	0.86-1.84	0.247	23
	Stage I	–	–	–	0
Ki-67 index	≥90%	1.73	1.30-2.29	<.001	56
	<90%	–	–	–	0
CD5 express	Positive	2.35	1.56-3.54	<.001	87
	Negative	–	–	–	0
BCL6 express	Positve	0.72	0.55-0.95	0.019	33
	Negative	–	–	–	0
β2-MG	Elevated	1.76	1.35-2.29	<.001	57
	Normal	–	–	–	0

Conclusions: The proposed nomogram provides an individualized risk estimate of OS in patients with DLBCL, especially for the patient who received R-CHOP like regimen.

Clinical trial identification: This project was approved by the Ethics Committee of Cancer Hospital, Chinese Academy of Medical Sciences.

Legal entity responsible for the study: National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1006PD Does the omission of vincristine affect outcome and survival in patients with diffuse large B-cell lymphoma?

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Background: The current standard treatment for diffuse large B-cell lymphoma (DLBCL) is Rituximab-CHOP (cyclophosphamide (CPM), doxorubicin(DXR), vincristine(VCR), prednisolone). It is well known that VCR causes peripheral neuropathy and is often dose-reduced or omitted from the treatment. Whether the omission of VCR from 1 or more cycles of therapy could jeopardize the survival of patients with DLBCL has not yet been adequately addressed. Our study aimed to investigate any differences in progression free (PFS) and overall (OS) survival in R-CHOP treated patients with DLBCL between those with omission of VCR or not.

Table: 1006PD

	PFS		OS	
	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Age ≥ 60	Not included		1.94 (1.09-3.48)	0.025
Treatment[a]	Not included		1.76 (0.90-3.43)	0.096
PS ≥ 2	1.62 (0.74-3.57)	0.235	1.77 (0.84-3.74)	0.134
Stage > 2	2.04 (1.01-4.00)	0.047	1.59 (0.88-2.88)	0.127
IPI > 2	1.33 (0,70-2.50)	0.385	1.14 (0.60-2.17)	0.686
LDH > ULN	1.09 (0.63-1.89)	0.778	1.03 (0.63-1.69)	0.893
Bulky[b]	1.30 (0.81-2.10)	0.283	1.58 (1.03-2.42)	0.037
Oncovin omission[c]	1.21 (0,76-1.95)	0.421	1.12 (0.75-1.69)	0.571
Extranodal[d] >1	1.02 (0.59-1.78)	0.932	Not included	
Kidney/Adrenal[e]	1.72 (0.78-3.85)	0.171	2.45 (1.20-4.98)	0.014
BMI ≥ 25	0.89 (0.58-1.37)	0.591	0.98 (0.67-1.43)	0.904
DoxoRDI ≤ 70%	1.88 (0.97-3.67)	0.063	2.04 (1.15-3.57)	0.014

Methods: In this Swedish multi-institutional, retrospective, cohort study we included all adult patients diagnosed with and primarily treated for DLBCL or subgroups of high-grade malignant B-cell lymphoma with either R-CHOP/CHOEP (CHOP plus Etoposide) or mini-CHOP (dose-reduced), between 2000-2013. All information on patients' characteristics, treatment outcome, and survival was extracted from the in-hospital computer based systems. Any clinical variables significantly associated with PFS or OS in univariate analysis by the log-rank test were considered for entry into a multivariate Cox proportional hazard regression model. Omission of VCR was included in all models as an independent variable of interest. All statistical analyses were performed with IBM SPSS statistics version 22.

Results: In total 541 patients were included in the study cohort. In 95 (17.6%) patients, VCR was omitted due to toxicity. The omission was more often decided during the last 3 cycles of chemotherapy (86 patients, 90.5%). Univariate analysis revealed 9 potential prognostic factors associated with PFS and 10 with OS. Omission of VCR was not associated with either PFS or OS in both univariate and multivariate analyses (HR for PFS: 1.21, 95% Confidence Interval (CI) 0.76-1.95; HR for OS; 1.12, 95% CI 0.75-1.69). For PFS only advanced stage at diagnosis was found to be significantly associated with worse outcome ($p = 0.047$). In respect of OS kidney/adrenal involvement ($p = 0.014$), Doxorubicin –RelativeDoseIntensity<70% ($p = 0.014$), age ≥60 years ($p = 0.025$) and bulky disease ($p = 0.037$) were significant predictors of survival.

Conclusions: Omission of VCR does not affect either PFS or OS in patients with DLBCL treated with R-CHOP/CHOEP. As a result, clinicians can safely decide to omit VCR in case of severe neurotoxicity due to VCR. Considering the association of bulky disease and kidney/adrenal manifestation of lymphoma on survival, further studies should focus on whether the treatment options for these subgroups need to be individualized. Finally, clinicians should be aware of the importance of giving adequate dose of DXR during treatment given the growing body of evidence on the role of dose intensity on survival.

Legal entity responsible for the study: Charlott Mörth

Funding: Centre for Clinical research Sörmland, Uppsala university

Disclosure: All authors have declared no conflicts of interest.

1007PD Preliminary results of novel safety interventions in adult patients (pts) with relapsed/refractory acute lymphoblastic leukemia (R/R ALL) in the ZUMA-3 Trial

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Background: Outcomes for adult pts with R/R ALL are poor. Promising results were observed with axi-cel (KTE-C19), an anti-CD19 chimeric antigen receptor (CAR) T cell therapy, in B cell malignancies (Locke et al. AACR 2017, #9986). Severe cytokine release syndrome (CRS) and neurologic events (NE) have been observed in pts with R/R ALL who received anti-CD19 CAR T cell therapy.

Methods: Eligible pts were aged ≥18 years with R/R ALL (Ph+ pts eligible), >5% bone marrow (BM) lymphoblasts, ECOG status 0-1, and adequate organ function. Pts received 1 or 2 × 106 CAR T cells/kg after conditioning (cyclophosphamide + fludarabine). Phase 1 primary endpoint was incidence of dose-limiting toxicity (DLT). Secondary endpoints were efficacy outcomes.

Results: As of 12/31/2016, 12 pts were enrolled; 11 received KTE-C19. One pt was excluded due to a serious adverse event (SAE) prior to dosing. Pts were 64% men, had 56-100% BM lymphoblasts before conditioning and 64% vs 36% had relapsed vs primary refractory disease. No DLTs were observed in the DLT-evaluation period of this trial. Of the first 6 pts enrolled at the 2 × 106 dose, 1 experienced Gr5 CRS. No KTE-C19-related Gr5 AEs were observed at 1 × 106 dose in 5 subsequent pts. Overall, the most common Gr ≥ 3 AEs were cytopenias (64% thrombocytopenia, 55% neutropenia). Gr ≥ 3 CRS and NE were reported in 27% and 55% of pts. Tocilizumab (toci) or steroids was given for AE management in 10 and 7 pts, respectively. All CRS (except 1 Gr 5) and NE resolved. Of the 10 efficacy-evaluable pts, 9 (90%) achieved minimal residual disease-negative remission (8 CR or CR with partial/incomplete hematopoietic recovery; 1 blast-free hypoplastic/aplastic BM). Median follow-up was 3.8 mos; 3 pts relapsed: 2 CD19- and 1 CD19+ disease. Efficacy was similar across KTE-C19 doses. To refine dosing and AE management, additional pts were treated with lower CAR T cell doses and received prophylactic toci. Clinical outcomes and translational data from these pts will be presented.

Conclusions: KTE-C19 demonstrates promising efficacy with a manageable safety profile for adult R/R ALL pts. Novel approaches to reducing toxicity, namely CRS and NE, may improve the overall risk: benefit profile for this class of therapies.

Clinical trial identification: NCT02614066

Legal entity responsible for the study: Kite Pharma

Funding: Kite Pharma

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1008PD ZUMA-4 preliminary results: phase 1 study of KTE-C19 chimeric antigen receptor T cell therapy in pediatric and adolescent patients (pts) with relapsed/refractory acute lymphoblastic leukemia (R/R ALL)

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Background: ALL is the most common childhood malignancy; up to 20% of pts relapse after initial therapy, and have poor clinical outcomes (Hoffman and Gore. Front Oncol 2014). Promising results were observed with KTE-C19, an anti-CD19 chimeric antigen receptor (CAR) T cell therapy, in B cell malignancies (Locke at al. AACR 2017, #9986). We present preliminary ZUMA-4 phase 1 results.

Methods: Pts aged 2-21 y with R/R ALL and adequate organ function received the planned dose of 1 or 2×10^6 CAR T cells/kg after low-dose conditioning chemotherapy (cyclophosphamide/fludarabine, CyFlu). Pts enrolled after the study's dose-limiting toxicities (DLTs) portion receive tocilizumab ≤36 h after CAR T cell infusion. Phase 1 primary endpoint is the incidence of DLTs. Secondary endpoints include efficacy and biomarker assessments.

Results: As of Dec 31, 2016, 4 of 5 enrolled pts have been treated; median follow-up, 5.3 mo (1.9-8.6). All pts had ≥2 prior lines of therapy and 1 pt had prior stem cell transplant (SCT). All pts received bridging chemotherapy due to high disease burden (baseline blasts, 41-99%) prior to KTE-C19. KTE-C19 was successfully manufactured in a centralized 6-7 d process across a range of baseline absolute lymphocyte counts (0.5–17.1 × 10^9/L) and CD4:CD8 ratios (0.1-0.7). KTE-C19 could not be manufactured for 1 pt who progressed with WBC >150,000/μL at apheresis and <0.2% T cells in the apheresis collection. There were no DLTs. One pt had a gr 5 AE due to intracranial hemorrhage from disseminated mucormycosis. All pts had cytokine release syndrome (all ≤gr 3; all resolved with supportive care) and 1 pt had gr 3 neurologic events. All pts achieved MRD- remission (1 ongoing). One pt received SCT post-remission. Peak CAR T cell expansion was 1-2 weeks post-KTE-C19 infusion. Data from additional pts and implemented safety measures (eg, mandatory tocilizumab) will be presented.

Conclusions: KTE-C19 after low-dose CyFlu was tolerable and appears safe for further analysis in pediatric and adolescent pts with R/R ALL. KTE-C19 can induce deep remissions in heavily pre-treated pts with high disease burden. Based on these results, ZUMA-4 continues to enroll (NCT02625480).

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Legal entity responsible for the study: Kite Pharma

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Pharma. R. Jain: Patent/Employment/Stock Ownership: Kite Pharma. All other authors have declared no conflicts of interest.

1009PD Treatment patterns in elderly patients (pts) with acute myeloid leukemia (AML) in routine clinical care in the united states (US)

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Background: AML is a cluster of hematopoietic syndromes characterized by proliferation of immature myeloid cells in the bone marrow resulting in cytopenias. While prognostic indices may predict therapy response, no consensus exists regarding optimal therapy for elderly AML pts.

Methods: Newly diagnosed AML pts aged ≥60 years were retrospectively identified from a large US electronic medical record from 1/1/2008-7/31/2015. AML diagnosis included ≥1 inpatient or ≥ 2 outpatient claims with an AML ICD-9/10 code (the first record was the index date). First-line therapy (1LT) was defined as an AML-specific treatment initiated on/after the index date; a switch in agent triggered second-line therapy (2LT). Pts were followed until death, end of follow-up, or end of study (9/31/2015).

Results: Of 704 eligible AML pts, 398 received 1LT. Mean age was 70.6 years, 55.5% were male, and 19.1% had a Charlson comorbidity index score of ≥ 2. 1LT regimens included cytarabine-based induction 1LT (C-IC) in 54.3% (n = 216, combined with an anthracycline [ie, 7 + 3 or 7 + 3-like] in 87.5% of these), hypomethylating agents (HMAs) (azacitidine and decitabine) in 30.2% (n = 110), other cytotoxic IC (other-IC) in 8.5% (n = 34), and sorafenib in 1.0% (n = 4). 44 pts (11.1%) had record of stem cell transplant during 1LT for AML. A higher proportion of pts who received HMAs (67.3%) were ≥75 years of age compared to those receiving C-IC or other-IC (18.5%; 23.5%). Overall, 84 pts (23%) received 2LT, with C-IC still predominating (n = 37; 44.0%), followed by HMAs (n = 31; 36.9%) and other-IC (n = 15; 17.9%). At a median follow-up of 8.5 months (interquartile range: 3.2, 20.1) for all pts with 1LT, 59.6% (n = 237) had died. During follow-up for all treated pts, 78.6% (n = 313) received erythrocyte or platelet transfusion support with a mean number of unique transfusion service dates per patient of 12.3 (standard deviation: 15.9), and 38.9% (n = 155) received colony-stimulating factors.

Conclusions: Overall, the majority of AML pts who are ≥60 years of age are treated with C-IC. Age ≥75 years may influence choice of 1LT between HMAs vs IC. More research is needed to evaluate other factors in therapy selection and prognosis for the elderly AML population.

Legal entity responsible for the study: Takeda Pharmaceuticals

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1010P Event free survival at 24 months: A new endpoint in diffuse large B-cell lymphoma

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Background: The monoclonal antibody rituximab has changed the natural history of Diffuse Large B-cell Lymphoma (DLBCL). Recent data show that patients with DLBCL achieving EFS24 (event-free survival at 24 months) after treatment with immunochemotherapy have a normal life expectancy. We have explored what happens in our patient population.

Methods: We reviewed our database of patients with lymphoma treated between 1987 and 2011. We selected DLBCL patients who had received a minimum follow up of 5 years. We included 228 patients in the analysis; 100 had received rituximab based treatment and 128 did not receive any antibody. We studied the pattern of relapse and event-free survival at 12 and 24 months from diagnosis in both populations.

Results: Our data show that the pattern of relapse in DLBCL patients has changed in the post-rituximab era. There are fewer relapses (24% versus 33%, p = 0,04) but those who relapse do so earlier: 75% of relapse occur in the first two years and late relapse (after 5 years) are rare (less than 8%) in rituximab treated patients. Patients who achieve EFS12 have a better prognosis than patients who did not achieve it (80% OS 5 years versus 15%, p < 0,001) but patients who achieve EFS24 have a very good prognosis compared to patients who do not achieve EFS24 (p < 0,001), regardless of the treatment received (90% versus 15% OS at 5 years, p < 0,001). Comparing EFS12 and ESF24, ESF24 is a better prognostic tool to determine long term survival.

Conclusions: Most of the patients who relapse after immunochemotherapy do so early, probably linked to a different biological behavior of the tumor. Patients who achieve EFS24 have a very good prognosis. We need to perform an accurate follow up with patients in the first 2 years after diagnosis to detect early relapses and focus on studying the molecular biology of these tumours to detect differences in relapsed patients. Follow up after 5 years from diagnosis will detect only a small account of relapses and probably will not impact on survival.

Legal entity responsible for the study: Hospital Puerta de Hierro Majadahonda

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Disclosure: All authors have declared no conflicts of interest.

1011P Interpreting progression-free survival and overall survival data in biosimilar clinical studies: considerations based on a recent rituximab biosimilar study

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Background: Oncology trials often report data on progression-free survival (PFS) or overall survival (OS), but such endpoints are prone to be less sensitive than short-term overall response (ORR) for confirming biosimilarity when long median PFS or OS are expected. We outline considerations when interpreting survival data with a sensitivity analysis from a recent rituximab biosimilar study.

Methods: A confirmatory phase III study compared the efficacy of the EMA approved biosimilar rituximab, GP2013 (n = 314) with reference rituximab (R) (n = 315) in patients with previously untreated, advanced follicular lymphoma. Patients received CVP chemotherapy during induction and responders received GP2013 or R maintenance monotherapy. Primary endpoint was equivalence of ORR at the end of induction. Secondary endpoints included PFS and OS, and hazard ratios (HRs) were estimated by a Cox proportional hazard model, with treatment allocation as the main effect and FLIPI score as a stratification factor.

Results: As of 31 Dec 2016, the median follow-up was 23.6 and 24.2 months for GP2013 and R, respectively. Equivalence criteria for the primary endpoint were met, confirming biosimilarity. For time-dependent endpoints, there was a high level of censoring without PFS (~70%) or OS (~90%) events. Median PFS or OS could not be estimated. HRs for PFS and OS were 1.31 (90% CI [1.02–1.69]) and 0.77 (90% CI [0.49, 1.22]), respectively. Kaplan-Meier analysis showed that PFS survival curves diverged between 12–24 months yet ran parallel outside this period, violating the proportional hazards assumption of the Cox proportional hazard model. Complete response (CR) rates were similar between treatments at all time points, including 33 months.

Conclusions: Small sample size, low event rate, data immaturity and/or other aspects of study design can subject survival analyses to chance findings and decrease sensitivity for biosimilarity assessments. In this study, HRs for PFS and OS had opposite directions and CR rates between treatments were similar across time, emphasizing these challenges. The PFS and OS results should be interpreted with caution as they may not reflect a difference, or lack thereof, between treatments.

Clinical trial identification: NCT01419665

Legal entity responsible for the study: Hexal AG, a Sandoz company, part of the Novartis group

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1012P Role of prephase treatment prior to definitive chemotherapy in diffuse large B -cell lymphoma (DLBCL)

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Background: Treatment related toxicity during the treatment of Diffuse large B cell lymphoma (DLBCL) is highest during the initial phase of treatment (First cycle effect). The toxicity can be febrile neutropenia, tumour lysis syndrome, deterioration in performance status and death. Introduction of prephase treatment is popular method to reduce this toxicity. This study was undertaken to evaluate the benefit of prephase treatment in Indian patients.

Methods: This was a prospective study carried out at Kidwai memorial institute of oncology Bangalore, India from July 2015 to December 2016. The newly diagnosed patients of DLBCL, age>18years, stage II-IV were enrolled in study. Written consent taken from all patients before starting chemotherapy (CHOP/R-CHOP). Out of 50 patients, 25 patients received prephase treatment consisting of vincristine (1 mg) on -6th days and prednisone 100 mg daily for 7 day (-6 day to day 0). All patients received CHOP/R-CHOP chemotherapy on day 1. ECOG performance status, nadir absolute neutrophil count (ANC) on day 10, febrile neutropenia, and hospitalization, requirement of

antibiotics and mortality within 30 days of chemotherapy were compared in both the groups. Patients above 60 years received prophylactic growth factor.

Results: The median age of the patients were as 50.5 years (Range 20-74 years). Thirty patients were male and twenty patients were female. Twenty patients (40%) had stage 2 disease while the other 60% patients had stage 3 or stage 4 disease. Most of the patients (96%) attanined ECOG performance status of 0 or 1 after prephase treatment. The incidence of any grade neutropenia on D10 of chemotherapy in experimental arm was 44% (88% in control arm) while the grade 3/4 neutropenia was 12% (48% in control arm). Febrile neutropenia in the experimental arm was lower (12%) as compared to control arm (32%) (p value<0.05). The mortality within 30 days remains same (4%), in both the arms.

Conclusions: Prephase treatment significantly improves the performance status of DLBCL patients prior to receiving chemotherapy (CHOP±Rituximab). First cycle effect, including decrease chances of febrile neutropenia and improvement in nadir ANC are impressive benefits of prephase treatment.

Legal entity responsible for the study: Kidawai memorial institute of oncology Bengaluru India

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1013P The role of FDG-PET/CT in detecting bone marrow involvement in diffuse large b-cell lymphoma

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Background: The sensitivity and prognostic value of FDG-PET/CT in the staging of Diffuse Large B-Cell lymphoma (DLBCL) remain unclear. PET/CT provides a high level of accuracy for identifying focal skeletal marrow disease in Hodgkin's lymphoma (HL). Whether the omission of staging Bone Marrow Biopsy (BMB) would change treatment strategy of DLBCL is not known.

Methods: We retrospectively studied 114 patients with DLBCL from three rural community oncology practices in New Mexico between January 96- September 2016. Patients receiving BMB and PET/CT were included. Descriptive statistics and Chi-square methods were used to evaluate associations.

Results: Mean age at diagnosis was 66 years (23-92), 54% were males, 82% received RCHOP therapy. Out of 114 patients, 27 (23%) patients did not have a staging BM biopsy. The sensitivity of PET/CT scan was 73% and Specificity 87%. Positive predictive value (PPV) 50% and Negative predictive value (NPV) 95%. Patients with positive focal PET/CT were more likely (50% vs 5%), χ^2 (1, N = 74) = 19.9, (p < 0.001) to have a positive BMB in comparison those with negative PET/CT scan. There was correlation of bone marrow involvement with clinical stage IV (31%), III (13%), II (5%), I (0%), χ^2 (1, N = 74) = 10.14, (p = 0.02) and IPI score: High (14%), Int-High (40%), Low-Int (10%), Low (3%) %), χ^2 (1, N = 74) = 10.7, (p = 0.019). Cytopenia was not associated with BM involvement χ^2 (1, N = 74) = 1.37, (p = 0.242). The 5-year OS for PET/CT positive vs BM involved (38% [95%CI 14-61] vs 31% [95CI% 5-56] p = 0.69), and PET/CT negative vs BM uninvolved patients (44% [95%CI 32-55] vs 50% [95%CI 38-61] p = 0.46) were not statistically different.

Conclusions: PET/CT is valuable as having a high negative predictive value for detection of focal marrow involvement in DLBCL. This may help avoid BMB, especially if clinically early stage disease. Cytopenia did not predict marrow involvement. The long-term prognostic value of PET/CT is similar to that obtained by a bone marrow biopsy.

Legal entity responsible for the study: Kymera Independent Physicians

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1014P Evaluation of various prognostic scores and impact of cell of origin on survival in limited stage DLBCL: retrospective study

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Background: Utility of International Prognostic Index (IPI) as standard prognostic tool in limited stage diffuse large B-cell lymphoma (Li DLBCL) has been controversial. Variety of other prognostic scores have been proposed including Miller's stage modified IPI (M-IPI), NCCN-IPI (N-IPI), and stage adjusted IPI (St-IPI). We aimed to compare various prognostic scores. In addition, data is not clear regarding impact of cell of origin (COO) i.e. Germinal Center (GCB) and non-GCB COO in patients with Li DLBCL. Our aim is to identify difference in outcomes by COO.

Methods: All patients with newly diagnosed non-bulky Li DLBCL treated with standard first line CHOP±R chemotherapy with or without radiation from 1987 to 2013 were eligible. Discrimination ability of each prognostic model was also tested using bagging model. Model performance was evaluated using sensitivity, accuracy and Area under the Receiver Operating Characteristic Curve (AUC) and model which scored highest AUC, was selected. Survival times and survival proportions were estimated using the Kaplan Meier survival curves. In addition, we applied Hans's algorithm to study prognostic impact of COO.

Results: The median age of the 276 included patients was 47 years. 32% received limited combine modality treatment while 68% patients received extensive chemotherapy. Median follow up was 4.9 years. M-IPI was the best prognostic indicator of both PFS (AUC=0.67) and OS (AUC=0.72) when compared with IPI, N-IPI and St-IPI. Immunohistochemistry data of 152 patients treated homogeneously was available to determine COO. GCB phenotype seen in 61%. There was no significant difference in PFS (p = 0.6) or OS (p = 0.4).

Table: 1014P Comparison of prognostic models for Li DLBCL

Risk model	Sensitivity		F-statistical		AUC	
	PFS	OS	PFS	OS	PFS	OS
St-IPI	0.92	0.91	0.69	0.68	0.59	0.58
IPI	0.47	0.51	0.57	0.60	0.61	0.64
N-IPI	0.81	0.84	0.66	0.68	0.58	0.6
M- IPI	0.73	0.6	0.68	0.64	0.67	0.72

Conclusions: Our data identified that in limited stage non-bulky DLBCL, M-IPI is more robust tool for outcome prediction with better power for risk stratification in the CHOP±R as compare to other prognostic models. There was no significant difference in PFS or OS for patients in the GCB and non-GCB limited stage non-bulky DLBCL.

Legal entity responsible for the study: Oncology Center, King Faisal Specialist Hospital and Research Center

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Disclosure: All authors have declared no conflicts of interest.

1015P The prognostic impact of serum albumin and absolute neutrophil count in patients with newly diagnosed diffuse large B-cell lymphoma

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Background: Patients (pts) with diffuse large B cell lymphoma (DLBCL) are treated with immunochemotherapy and are generally stratified by the NCCN International prognostic index (NCCN-IPI). It has been reported that some host-related factors such as nutritional status (NS) and systemic inflammation (SI) were associated with the outcome of pts with solid tumors. However, data regarding their prognostic contribution in DLBCL are limited. Therefore, we decided to access the possible prognostic significance of some laboratory markers associated with NS/SI in DLBCL pts.

Methods: We retrospectively reviewed the clinical outcome of 251 R-CHOP treated DLBCL pts. A receiver operating characteristic (ROC) curve analysis was used to illustrate the best cut off values of the serum albumin (SA), beta-2-microglobulin, absolute neutrophil (ANC), lymphocyte, monocyte and platelet counts, and hemoglobin level to predict overall survival (OS) by Kaplan-Meier method in our data set.

Results: The estimated 5-year OS of the whole group was 61%. The multivariate analysis showed that only SA and ANC remained independent predictors of OS by applying the best cut off values determined by ROC - 39.4 g/L and 5.33 x 10^9/L, respectively. Furthermore, the combination of dichotomized SA and ANC generated a prognostic index (SA/ANC PI) that stratified patients into 3 different risk groups: low risk [LR] (SA > 39.4 g/L and ANC ≤5.53 x 10^9/L), intermediate risk [IR] (SA > 39.4 g/L or ANC ≤5.53 x 10^9/L), and high risk [HR] (SA ≤ 39.4 g/L and ANC >5.53 x 10^9/L). The 5-year OS for LR, IR and HR pts was 86%, 65.7% and 22.5% (P < 0.001), respectively, and our PI was independent of the NCCN-IPI.

Conclusions: Our data showed that SA/ANC PI could predict OS in DLBCL pts and may present a reliable, convenient and sensitive predictor to identify pts with poor prognosis in addition to NCCN-IPI.

Legal entity responsible for the study: Specialized Hospital for Active Therapy of Hematological Diseases

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1016P Autologous stem cell transplantation (ASCT) is safe and effective for the treatment of non-hodgkin lymphoma (NHL) in an elderly population of patients over 65 years old: A single center experience

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Background: High-dose chemotherapy followed by ASCT is a widely used treatment for agressive or recurrent NHL for young patients (pts). Limited data are available on the feasibility and the results of this strategy for older pts, who are often excluded from agressive treatment. This study aimed at comparing pts ≥65 years old(yo) to a younger pts' population in term of tolerance, safety and results of ASCT.

Methods: We did a retrospective study in one center in France. We included every consecutive pts treated by ASCT for NHL from May 2007 to January 2016. We collected data on the characteristics of the pts and their disease, previous treatments, and tolerance and outcome after ASCT.

Results: 48 pts ≥ 65 yo (mean: 49.5) and 129 < 65 yo (mean: 68.7) at the time of the transplant were included. The most common histology was diffuse large B cell lymphoma ($p = 0.205$). There were only 2 differences between the 2 groups. First, the number of pts with comorbidities was higher in the elderly population ($p = 0.016$), especially cardio-vascular ($p < 0.001$). Secondly, the moment of the ASCT was mainly on first line for young pts *vs* at the time of relapse for older pts ($p < 0.001$). At the time of ASCT, in both groups ($p = 0,306$), a majority of patients were in complete response. No differences were found between the 2 groups for the conditionning regimen, number of $CD34^+$ cells reinjected, number of transfusion, weight loss, length of the hospital stay and duration of aplasia. There were no differences of grade ≥3 toxicities (hematologic, infections, digestive, renal, cardiac, mucositis.) for both groups ($p = 0,116$). Treatment Related Mortality (death within 30 days following ASCT) was: 2% for pts ≥65yo vs 3.9% ($p = 1$). The mean follow-up time was 56 months for young pts vs 77 months for older ($p < 0.001$). The specific survival was similar between the 2 groups, 65% for the young pts group vs 72% for the older ($p = 0.63$) 3 years after ASCT.

Conclusions: High-dose chemotherapy followed by ASCT is as safe and effective in a population of pts ≥65 yo compared to a younger population. Agressive treatment could be considered earlier in the management of elderly pts and should not be excluded only depending on the age of the patient.

Legal entity responsible for the study: Centre antoine Lacassagne

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1017P Phenotypic and functional characterization of tumor infiltrating lymphocytes (TIL) grown from non-hodgkin lymphoma tumors: Implications for the development of novel therapies for lymphoma

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Background: Cell therapy with TIL is an effective treatment with acceptable safety profile for advanced metastatic melanoma patients. TIL products can be centrally manufactured for broad clinical application. Adoptive cell therapy with TIL involves collection of autologous lymphocytes from the tumor via surgical resection, ex vivo expansion of TIL, lymphodepletion of the patient prior to infusion of TIL, followed by infusion of TIL and treatment with IL-2. Here, we present findings related to expanding TIL directly from lymphoma.

Methods: Using methods for TIL isolation and growth developed at Lion, we expanded TIL from 5/5 lymphoma (1 MCL, 3 follicular, 1 DLBCL) with Interleukin 2 for 11-14 days and subsequent rapid expansion for 14 days using mitogenic anti-CD3 antibody and irradiated allogeneic PBMC.

Results: TIL were generated from all 5 lymphoma tumors with a maximum expansion index of 680-fold, significantly higher than previously reported. Mean CD3+ T cell population was 95% (vs 75% previously reported). As with TIL expansion from melanoma, we observed a marked relative increase in effector memory cells in lymphoma TIL. A significant increase in TEMRA ($p = 0.0013$; CD4, CD8) and CD28+CD4+ ($p = 0.008$) subsets was observed in lymphoma compared with melanoma TIL cultures. Bioluminescent Redirected Lysis Assay (BRLA) to assess TIL cytolytic activity at 4 hrs ranged from <1-6 LU_{50} in lymphoma TIL compared to melanoma TIL (11-75 LU_{50}, 4hrs). ELISpot and ELISA analysis revealed IFN-γ production by lymphoma TIL comparable to that of melanoma TIL. Consistent with the observation that lymphoma-reactive T-cells are primarily TH2 and TH17, nanostring analysis revealed that lymphoma TIL expressed higher levels of RORC and IL17A than melanoma TIL.

Conclusions: We demonstrate here the feasibility of growing TIL from lymphoma that have effector functions comparable to that of melanoma TIL. These findings serve as a rationale for considering TIL cell therapy for patients with lymphoma.

Legal entity responsible for the study: Lion Biotechnologies, Inc

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1018P International prognostic scores (IPS-7, IPS-3 and IPS-3 new) for prediction of FFS and OS in cases with Hodgkin Lymphoma. Which is more practical and accurate?

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Background: Hodgkin Lymphoma (HL) is one of the curable malignant diseases. International prognostic score7 (IPS-7) was a valuable scoring system predicting FFP and OS in cases with HL. A simpler prognostic score: IPS-3 has been proposed 2 years ago and in this scoring system age and stage were found to be significant for FFP and age, stage and hemoglobin were found to be significant for OS. Here we evaluated IPS-3 new system in cases with HL.

Methods: 364 patients with HL treated by ABVD have been included in this study. Two thirds of the patients had nodular sclerosing type HL, 76 had mixed cellularity type. Median follow up was 71 months.

Results: Seven clinical parameters on the basis of the IPS-7 determined to be associated with adverse clinical outcome were evaluated. The prognostic ability of seven IPS factors was evaluated for both FFP and OS. A new 3-factor prognostic score (IPS-3 new) was constructed utilizing factors that were significant in multivariate Cox models: age>45 years, stage IV disease and lymphocytopenia were found to be independent factors. Thus IPS-3-new was constructed utilizing these 3 factors that were significant in multivariate Cox models. Lymphocytopenia was used instead of hemoglobin <10.5g/dl that has been recommended for IPS-3 score. The prognostic performance of IPS-7, IPS-3 and IPS-3-new was evaluated. Patients classified into 3 risk groups low, intermediate, and high risk. Specifically, for cases that were re-classified to different risk group by IPS-3-new, the observed FFP and OS estimates were compared to survival rates predicted by IPS-7 and IPS-3 respectively. An alternative prognostic index, the IPS-3-new, was constructed using age, stage, and lymphocytopenia (FFP: $p = 0.0001$ and OS: $p < 0.0001$).

Conclusions: The IPS-3 new covering lymphocytopenia instead of anemia besides age and stage factors on risk prediction for FFS and OS may provide a more accurate and reliable framework for risk assessment for the patients with HL.IPS-3 new is important due to the predictive property of lymphocytopenia in HL in immunotherapy era.

Legal entity responsible for the study: Semra Paydas et al

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Disclosure: All authors have declared no conflicts of interest.

1019P Evaluation of indoleamine 2,3-dioxygenase expression (IDO), transforming growth factor beta (TGF-β) and interleukin 13 (IL13) expression on clinical outcome in patients with Hodgkin's lymphoma

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Background: Nowadays, patients with Hodgkin's lymphoma (HL) have a high cure rate. However, approximately 20% pts have relapse or progressive disease. The main histological feature in HL is presence by Hodgkin Reed-Sternberg (HRS) cells. HRS cells produce a diversity of cytokines and chemokines. There is still a limited information of prognostic role expression of cytokines in patients with HL. We assessed the impact on clinical outcome of the IDO, TGF- β and IL-13 expression in patients with HL.

Methods: 79 patients (pts) with HL were included in this study (median age: 41, range: 18-65 years; males: 26, females: 53). Early stages of HL have 53.3% and 46.7% pts had advanced stages. Patients were treated with ABVD or BEACOPP (14/esc) and radiation therapy. CR/PR was achieved in 86.1% of patients. 13.9% of pts had relapse or disease progression during the therapy. mRNA expression levels of IDO, TGF-β, IL-13 were measured in fresh pre-treatment tumor tissue specimens from HL patients using real-time qPCR analysis.

Results: 25 pts (31.6%) had IDO positive expression (IDO^+) and 54 (65.4%) pts was IDO negative (IDO^-). Multivariate analysis showed that IDO^+ expression correlated with worser EFS rate with HRs of 10.7 [95% confidence interval(CI) 0.4–0.6, $p = 0.01$], especially in 3-years EFS in IDO^+ males comparing to IDO^+ females (61% vs 71%, $p < 0,05$). We did not find significant corellation between such signs as B-symptoms, stages, response reate and IDO expression ($p = 0.14$). Expression of IL13 and TGF was performed in 69 pts. We divided patients in two groups: $IL13^+$ (high expression) vs. $IL13^-$ (low expression) and $TGF\text{-}\beta^+$ (positive expression) vs $TGF\text{-}\beta^-$ (negative expression). Number of pts with $IL13^+$ were 34 (49.3%) and 35 (50.7%) with $IL13^-$, while 47

pts were TGF-β^+ were (68.1%) and 22 pts (31.9) had TGF-β^- expression. It was found, that patients with high IL13 expression had worse EFS and OS rate compared to pts with low IL13 expression. 5-year EFS in patients with $IL13^-$ was 98% vs 65% in $IL13^+$ ($p < 0,05$), as well as 5 year OS in $IL13^-$ and $IL13^+$ groups was 98% and 87%, respectively ($p < 0,05$). Patients with TGF-β^- expression had better 5-years OS: 99% in pts with TGF-β^- vs. 87% TGF-β^+ pts ($p < 0.05$). We also analyzed two groups of double-positive (IDO^+/TGF-β^+) and double-negative(IDO^-/TGF-β^-) and three groups of pts with $TGF^+/IL13^+$ vs $TGF^-/IL13^-$ vs $TGF^+/IL13$ as potential prognosis biomarkers. ROC-analysis showed that response rate in pts with IDO^-/TGF-β^- was higher compared to IDO^+/TGF-β^+ pts ($p = 0.0001$). 5-years EFS rate was lower in pts from TGF-β^+/IL13+ group comparing to $TGF^-/IL13^-$ and $TGF^+/IL13^-$ groups and was 63% vs 99% vs 98% respectively ($p < 0.05$).

Conclusions: Our data showed that IDO, TGF-β and IL13 expressions have a role in predicting clinical outcome in pts with HL. Positive expression of IDO, TGF-β and high expression level of IL13 could be considered as a negative prognostic marker. Significantly worser outcome had pts with positive expression of two cytokines comparing with patients, who had only one positive marker.

Legal entity responsible for the study: T. Skrypets

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Disclosure: All authors have declared no conflicts of interest.

1020P Clinical impact of atypical phenotypes in adult t cell lymphoma/leukemia among HTLV carriers

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Background: ATLL represents a fatal disease epidemiologically linked to chronic infection with human T-cell lymphotropic virus type 1 (HTLV1). The diagnosis is classically described based on morphology, immunophenotype (typically CD7, CD8, CD56, ALK, EBV and PAX5 negatives). Our aim was to describe characteristics and compare outcomes between patients with classical ATLL and those with mature T-cell lymphoma and HTLV1 infection (atypical ATLL).

Methods: We reviewed 276 medical records from pts with HTLV1 infection and T-cell lymphomas diagnosed between 2008-2014 at the Instituto Nacional de Enfermedades Neoplasicas (Peru). Groups were divided based on presence of classical characteristics of ATLL, outcomes and survival differences were calculated by log-rank test in the univariate analysis and Cox regression analysis for prognostic factors.

Results: From 276 pts, 126 (45%) had classical ATLL phenotype and 150 (54%) were atypical. Mean age was 56 years and 19% were <45y, tuberculosis was presented in 32 pts (11.6%). Pts with classical disease had shorter length of disease (3.5 versus 5.6 months, $p = 0.01$), more B symptoms (51.6% vs 38.7%), bone marrow (51 vs 28%) and peripheral blood involvement (54 vs 32%) than pts with atypical ATLL. According to Shimoyama classification, acute subtype was most common in classical ATLL (46%), as Lymphoma most frequent subtype in atypical ATLL (54%). Most pts received a CHOP-based chemotherapy (71%) and overall response were 28% for classical ATLL (CR:15%, PR:12%) and 41% for atypical ATLL (CR:25%, PR:16%). At 5 years follow-up, median PFS were 2 months in classical and 4 months in atypical ATLL (HR: 1.30, 95%CI [1.02-1.67], $p = 0.036$), and median overall survival (OS) were 4 and 7 months for classical and atypical ATLL respectively (HR: 1.51, 95%CI [1.17-1.95], $p = 0.002$). In multivariate analysis, high levels of calcium and LDH, status performance and neutrophil-to-lymphocite ratio were independent prognostic factors for relapse and death.

Conclusions: It seems that there are atypical presentations of adult T cell lymphoma/leukemia with slightly better response to chemotherapy and survival, further studies with integration of viral RNA to neoplastic tissues are needed to confirm this category.

Legal entity responsible for the study: Instituto Nacional de Enfermedades Neoplasicas

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Disclosure: All authors have declared no conflicts of interest.

1021P Evaluation of the PI3K pathway in peripheral t-cell lymphoma

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Background: Peripheral T-cell lymphomas (PTCL) are a heterogeneous group of aggressive malignancies with dismal outcomes and limited treatment options. While the PI3K pathway has been shown to be activated in many B-cell lymphomas, its therapeutic relevance in PTCL is not clear. The aim of this study was to investigate the expression and activation of the signaling molecules in the PI3K pathway in each subtype of PTCL and to identify the potential therapeutic options for clinical testing.

Methods: The expression of PI3Kα, PI3Kβ, PI3Kγ, PI3Kδ, AKT1, pAKT1 and PTEN was analyzed in 88 PTCL samples by immunohistochemistry. This included all major mature T- and NK-cell neoplasms. Uni- and multivariate analyses were also performed using the expression and patients' clinical data.

Results: Staining for PI3Kα and AKT1 was positive in 86 (98%), PI3Kδ in 85 (97%), PI3Kβ in 79 (90%), PI3Kγ in 50 (57%) and pAKT1 in 45 (51%) samples. No PTEN staining was observed in 9 (10%) cases and the expression was weak in 70 (80%) samples. There were no correlations between expression and PTCL subtype. Patients with positive pAKT1 had higher IPI score ($P = 0.004$) and higher stage ($P = 0.02$). Loss and low expression of PTEN were associated with older age at diagnosis ($P = 0.02$). In the univariate analysis, high PI3Kα, older age, high IPI and high ECOG score were significantly associated with inferior OS and PFS ($P < 0.05$). In addition, low PI3Kδ (in contrast to PI3Kα), male gender and elevated LDH were also associated with worse PFS ($P < 0.05$). The median OS of patients with low PI3Kα was 25 months (95% CI: 14.8-67.0 months) compared to 11 months (95% CI: 1.8-16.3 months) in patients with high PI3Kα. For PFS, the median survival was 11 months (95% CI: 8.0- 17.6 months) for patients with low PI3Kα and 4 months (95% CI: 1.1-8.6 months) for patients with high PI3Kα. PI3Kα, age and IPI, and PI3Kα, gender, ECOG score and stage remained independent prognostic factors for OS and PFS, respectively, in the multivariate analysis ($P < 0.05$).

Conclusions: All 88 samples demonstrated at least partial activation of the PI3K pathway. High PI3Kα expression was an independent poor prognostic factor for both OS and PFS. This study provides evidence that targeting the PI3K pathway, particularly inhibition of PI3Kα, could be a promising approach for the treatment of PTCL.

Legal entity responsible for the study: Choon Kiat Ong

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1022P Safety and tolerability of chemotherapy (CT) containing high doses of methotrexate (HD-MTX) and cytarabine (Ara-C) in patients with primary central nervous system lymphoma (PCNSL) and hepatitis B virus (HBV) infection

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Background: HBV reactivation is a serious complication of some anticancer therapies. Preliminary studies suggested high rates of HBV reactivation, with fatal outcome, in pts with PCNSL treated with standard HD-MTX-based CT. Risk of HBV reactivation is further increased by the use of Rituximab (Rtx), which significantly improves efficacy of CT in PCNSL. Hence, HBV-positive pts are usually excluded from prospective trials, with a negative effect on accrual, and are treated with less intensive therapies, resulting in lower cure rates. Herein, we report the incidence of HBV infection and reactivation in a mono-institutional series of PCNSLs treated with modern strategies.

Methods: HIV-negative pts with newly diagnosed PCNSL treated with CT containing HD-MTX and Ara-C ± rituximab at our Institution, from 2010 to 2016, were analyzed to establish incidence of HBV infection, hepatotoxicity and treatment-related viral reactivation.

Results: 48 pts (median age 58, range 29–76) were considered. Eight (17%) pts had "resolved" HBV infection (negative HBsAg but positive anti-surface [anti-HBs] or anti-core [anti-HBc] Antibodies), one (2%) pt had active infection. HBV prophylaxis with lamivudine was indicated in 3/8 pts with resolved HBV. The pt with active infection was treated with entecavir. Induction comprised HD-MTX plus Ara-C in 2 pts, HD-MTX, Ara-C and Rtx in 2, and HD-MTX, Ara-C, thiotepa and Rtx in 5 (MATRix). Transient grade 1-2 elevation of hepatic enzymes (AST, ALT, GGT) was observed in all pts; grade 3-4 was recorded in 17/39 (44%) HBV-negative pts and in 5/9 (56%) HBV-positive pts (Fisher exact; $p = 0.71$). Eight out of 9 HBV-positive pts received the 4 planned CT courses without dose reductions due to hepatotoxicity; six pts achieved a CR and received consolidation (WBRT 2, ASCT 3, lenalidomide maintenance 1). At a median follow-up of 27 months for the whole series (12-88), no pt experienced HBV reactivation during first-line treatment, 5 pts remain relapse-free.

Conclusions: This study suggests that MTX-Ara-C-based therapy, MATRix regimen, in particular, can be safely used in PCNSL pts with HBV infection, without impaired life expectancy.

Legal entity responsible for the study: IRCCS San Raffaele

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Disclosure: All authors have declared no conflicts of interest.

1023P 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

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Background: Temsirolimus (TEM), an mTOR inhibitor, is approved in the EU for the treatment of pts with rel/refr MCL. A pivotal study demonstrated significantly longer progression free survival (PFS) with TEM (175 mg weekly for 3 weeks followed by 75 mg weekly) in rel/refr MCL pts compared to investigator's choice therapy (4.8 vs 1.9 months (mo); P = .0009). To evaluate the safety profile and efficacy of TEM in this rare tumor entity, further data collection in an unselected routine clinical patient population is useful.

Methods: A German multicenter registry for rel/refr MCL pts treated with TEM was started in Germany in Oct 2009 with regulatory and ethic committeés approval. Objectives are the evaluation of the safety profile, tolerability and anti-tumor activity of TEM as well as patient's profile including comorbidities, characteristics, and the sequence of systemic therapies.

Results: From Oct 2009 to Feb 2017, 55 pts were recruited in 30 study sites. Baseline characteristics are available for 55 pts: 69.1% male; median age 74.4 years; bone marrow involvement in 38.2% of the pts; ECOG PS (n = 54) 0 or 1 in 83.3%, ECOG PS 2 in 16.7%. According to MIPI score (n = 53), 20.8%, 34.0%, and 45.2% are classified as low, intermediate, and high risk at the time of enrollment. Median number of prior therapies is 2 with 43.6% treated in $\geq 4^{th}$ line. Most common drug-related toxicities of any grade (incidence $\geq$ 15%) are observed in following categories: blood/lymphatic system disorders (49.1%), gastrointestinal disorders (27.3%), general disorders (21.8%), and skin/subcutaneous tissue disorders (18.2%). Efficacy analyses are available for 39 assessable pts with an objective response in 30.8%, a clinical benefit (CR, PR, MR and SD) in 59.0% and PD in 41.0% of the pts. Median PFS for all pts is 3.6 mo. For the subgroup of pts treated with TEM in 2^{nd} and 3^{rd} line PFS is 3.3 mo, for $\geq 4^{th}$ line pts 4.9 mo.

Conclusions: The registry was started to evaluate the safety and efficacy of TEM in pts with rel/refr MCL in routine clinical practice. In this comparatively poor-prognosis patient population, TEM showed a predictable, manageable tolerability profile. Efficacy parameters were consistent with published phase III data.

Clinical trial identification: NCT00700258

Legal entity responsible for the study: Pfizer Pharma GmbH

Funding: Pfizer Pharma GmbH

Disclosure: M. Dreyling, G. Hess: Consultant Pfizer Pharma GmbH, Honoraria from Pfizer GmbH. G. Krekeler: Employee of Pfizer Pharma GmbH.

1024P Clinical impact of FISH analysis in extramedullary plasmacytomas

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Background: Extramedullary plasmacytomas (EMPs) is a rare presentation of plasma cell neoplasm and accounts for 7 to 15% of all plasma cell neoplasm. Fluorescence in-situ hybridization (FISH)-detected abnormalities, including del(17p), del(13q), and t(4;14), have been associated with inferior prognosis. However, there are few data about the prognostic significance of cytogenetic abnormalities in multiple myeloma (MM) patients with extramedullary plasmacytoma (EMP). This study aimed the clinical features, FISH data and outcome of patients with EMPs.

Methods: The data were collected from 70 patients with EMPs, retrospectively. We excluded skeletal plasmacytomas. The clinic-pathologic variables and treatment outcome retrospectively reviewed.

Results: Seventeen patients had solitary EMPs. Most common site of solitary EMP was nasal cavity and most patients received radiotherapy (n = 7) and surgery (n = 6). A total of 905 patients with newly diagnosed MM were included, and 53 patients (8.7%) had EMPs at diagnosis. Thirty-three patients had conventional FISH data. By conventional cytogenetic analysis and FISH, 35.8% (19/53) and 54.5% (18/33) patients were identified genetic abnormalities, respectively. By comprehensive cytogenetic/FISH approach, the most common genetic aberration was 1q21 amplification and/or 1p32 deletion (42.4%, 14/33), followed by -13 or del (13q) (24.3%, 8/33), del (17p) (15.2%, 5/33), IGH/FGFR3 rearrangement (15%, 2/33) and IGH/CCND1 rearrangement (12%, 2/33). Patients with initial EMPs had significantly worse overall survival compared to those without initial EMPs. Del(13q), and t (4;14) have been associated with inferior prognosis.

Conclusions: In the current study, del(13q), and t (4;14) were associated with worse survival in MM patients with EMP.

Legal entity responsible for the study: Hyun Ae Jung

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1025P Independent predictors of one year mortality in patients with primary systemic immunoglobulin light chain cardiac amyloidosis

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Background: Immunoglobulin light chain amyloidosis (AL amyloidosis) is a monoclonal plasma cell proliferative disorder that is characterized by tissue deposits of misfolded insoluble κ and λ light chain derived amyloid fibrils, leading to organ dysfunction. The prognosis of patients depends on the number and severity of organ involvement, especially cardiac involvement. Nearly half of the patients with amyloidosis die within a year of diagnosis. We analysed factors predicting early mortality (within one year) in patients with systemic immunoglobulin light chain cardiac amyloidosis.

Methods: Retrospective analysis of patients between January 2007 and January 2016 from our hospital database. In patients with AL cardiac amyloidosis, cardiac involvement was defined as per American society of echocardiography (ASE) criteria. We evaluated the clinical, ECG and ECHO parameters of early relapse (ER) within one year in these cardiac AL amyloidosis patients. Log rank test was done to identify independent predictors of one year all cause mortality.

Results: Among the 72 patients (mean age 58.2 + 8.2 years, 59.7% males) of AL amyloidosis with cardiac involvement, 32 (44.4%) died within one year. Sixty five patients (90%) received melphalan/thalidomide/bortezomib/cyclophosphamide/dexamethasone based chemotherapy as a monotherapy or in combinations. Logistic regression analysis revealed NYHA Class III/IV (p = 0.024), BNP (p = 0.031), Troponin I (p = 0.042), Free light chain difference (p = 0.011) and restrictive pattern of diastolic dysfunction ($E/E^1 > 20$) to be independent predictors of all cause mortality (p = 0.021). Kaplan Meir survival analysis showed a worse prognosis in patients with $E/E^1 > 20$ (Log rank, $p < 0.001$). In addition, in patients who completed atleast 6 months of chemotherapy, a decrease in E/E^1 (survivors delta E/E^1 5.2+ 0.8, nonsurvivors 0.8+ 0.3, p = 0.001) is associated with better one year survival.

Conclusions: AL Cardiac amyloidosis carries a poor outcome. Baseline Troponin I, NYHA class III/IV, difference in free light chain, restrictive pattern of diastolic dysfunction and BNP were the independent predictors of early mortality within 1 year in patients with AL cardiac amyloidosis. In patients who completed atleast 6 months of chemotherapy, a decrease in the ECHO parameter E/E^1 is associated with better one year survival. This will help us in better prognostication of patients with AL cardiac amyloidosis.

Legal entity responsible for the study: Amrita institute of medical sciences

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1026P Endoscopic evaluation of acute intestinal GVHD after allogeneic hematopoietic cell transplantation?

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Background: Acute graft versus host disease (GVHD) is a common complication of hematopoietic cell transplantation (HCT). The exact incidence is unknown due to the difficulties in diagnosis. The gastrointestinal tract (GIT) is one of the main target organs in patients with acute GVHD. There is also lack of consensus regarding whether upper or lower GIS endoscopy is required first and the site with highest sensitivity for biopsy.

Methods: All patients (111) with suspected intestinal GVHD were evaluated with upper GIS endoscopy or both upper and lower GIS endoscopy according to presenting symptoms. Biopsies were stained using hematoxylin-eosin and evaluated by the same experienced pathologist. The presence of apoptotic bodies, crypt/glandular abscesses and crypt/glandular destruction was considered confirming findings in histologic specimen for the diagnosis of GVHD. And the criteria proposed by Washington were used for histological grading of acute intestinal GVHD.

Results: Allogeneic HCT was performed in 111 patients of whom 27 (24.3%) had developed acute GVHD. Nineteen of the 111 patients with intestinal symptoms were evaluated for intestinal involvement, and 17 were diagnosed with acute intestinal GVHD. Upper endoscopic findings had a sensitivity of 64.7%, a specificity of 50%, a positive predictive value of 91.6% and a negative predictive value of 14.2%. The diagnostic accuracy of upper endoscopy was 63.1%. Lower endoscopic findings had a sensitivity of 40% and a specificity of 0%. The diagnostic accuracy of upper endoscopy with duodenal biopsy and sigmoidoscopy was 94.1%.

Conclusions: Endoscopic findings are nonspecific in acute intestinal GVHD. There is little agreement between endoscopic findings and histopathology; thus, biopsies are

essential. In patients with intestinal symptoms after HCT, upper endoscopy with duodenal biopsy and sigmoidoscopy has an acceptable diagnostic yield for intestinal involvement.

Clinical trial identification: Prospective study

Legal entity responsible for the study: Local ethics committee

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1027P Surveillance stool culture and its association with febrile neutropenia in patients with acute leukemia (AL) undergoing induction chemotherapy

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Background: Febrile neutropenia remains one of the major concerns of intensive chemotherapy and contributes significantly to morbidity, health care expenditure and mortality. Colonization of gut by MDR bacteria is regarded as a potential risk factor for subsequent infection with the same organism during febrile neutropenia. In this study, we aim to find the profile of surveillance stool culture and its association with febrile neutropenia in patients of acute leukemia undergoing induction chemotherapy.

Methods: Newly diagnosed patients of acute leukemia eligible for intensive chemotherapy were recruited for the study. Baseline stool microscopy and culture sensitivity was done to identify colonization with pathogenic bacteria. Blood and other samples were collected during febrile neutropenia. Association between surveillance stool culture and subsequent infections were studied.

Results: A total of 106 patients were recruited from November 2015 to March 2017. 59 patients were pediatric AL with median age of 10 years and 47 patients were adult AL with median age of 33 years. 68.86% of patients had gut colonization with bacteria of which 33.01% were MDR while 35.84% were non-MDR. Most common MDR bacteria colonizing gut were E. Coli (62.16%) and Klebsiella Pneumonia (21.82%). A total of 264 blood cultures were taken from 68 patients who developed 114 episodes FN during induction. Blood culture positivity rate was 17.80% with 68.08% of the isolates being MDR. Most common MDR isolates were Klebsiella (28.12%) and pseudomonas (18.75%). 34.28% of patients colonized with MDR bacteria developed MDR sepsis during induction compared to 23.68% non MDR colonizers. Induction mortality was 20% in MDR colonizers compared to 10.52% in non-colonizers.

Conclusions: Our study suggests that a significant proportion of patients are colonized with MDR bacteria and there is a high prevalance of MDR sepsis during induction. MDR sepsis and induction mortality were higher in patients colonized with MDR bacteria compared to non MDR bacteria.

Legal entity responsible for the study: JIPMER

Funding: JIPMER

Disclosure: All authors have declared no conflicts of interest.

1028P L-arginine – targeted for the anthracycline cardiotoxicity prevention in patients with acute leukemia of high cardiological risk

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Background: The risk of anthracycline cardiotoxicity (AC) significantly increases in patients with comorbid ischemic heart disease (IHD), which requires monitoring and prevention during chemotherapy (CT) of acute leukemia (AL). In this study we aim to evaluate the effectiveness of L-arginine in AC prevention in AL patients with comorbid IHD during induction CT.

Methods: A total 66 patients with newly diagnosed AL and comorbid IHD were included in the study, ECOG I-II. The cohort consisted of 34 (51.5%) males and 32 (48.5%) females, age 54-72 years. The IHD duration was 3–15 years. CT included doxorubicin. We determined the level of troponin I, nitrite anions $[NO_2]^-$, performed daily ECG-monitoring: at baseline and in achieving a cumulative dose of anthracyclines (CDA) from 100 to 200 mg/m^2. Depending on AC prevention patients were divided into two groups: I (n = 36) – AL patients treated with CT; II (n = 30) – AL patients treated with CT and L-arginine.

Results: Prior to CT, according to the daily ECG-monitoring in 47 (71.2%) patients' periods of tachycardia were diagnosed, with single supraventricular extrasystoles (SEs) and ventricular extrasystoles (VEs) – in 35 (53%) and 17 (25.7%) pts, respectively. The decreased concentration of $[NO_2]^-$ in blood serum in 1.5 times relative to normal values ($p<0.05$) was noticed. Troponin I in all patients of both groups was <0.5 ng/ml. Reaching low CDA in group I we recorded: periods of tachycardia in 36 (100%) pts, increasing number of single and paired SEs – in 24 (66.6%), VEs episodes – in 19 (52%), clinically significant ST-segment depression – in 29 (80.5%) and interval QT prolongation – in 14 (38.8%) pts. Troponin I was >0.5 ng/ml in 7 (19.4%) pts. Simultaneously, deepening of endothelial dysfunction (ED) was noted: $[NO_2]^-$ was in 1.8 times lower vs norm. After 2 CT courses in 20 (66.6%) patients of group II on tachycardia background the single SEs were recorded and only in 1 (3.3%) patient troponin I level was >0.5 ng/ml. The ED leveled: $[NO_2]^-$ didn't significantly differ from the norm.

Conclusions: Thus, L-arginine in AL patients with comorbid IHD during induction CT leads to reducing the risk of necrotic injury of cardiomyocytes and improves endothelial function that prevents early AC.

Legal entity responsible for the study: Ukrainian Medical Stomatological Academy

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1029P Multiple myeloma complicated by concomitant cardiac pathology

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Background: Patients with multiple myeloma (MM) often have cardiac comorbidities because of several factors, including the history of cardiac events, myeloma and treatment-related factors. Age is an important risk factor, given that the median age at the diagnosis of MM in Russia is 64 years. Additionally, the MM-related cardiac risk factors include underlying and undiagnosed cardiac amyloidosis, hyperviscosity, high-output failure, anemia and renal failure. Therefore, there are poorly understanding of real efficiency anti-myeloma treatment for this category of patients. In the presented work we have analyzed the efficiency of the most commonly used bortezomib-containing regimens in anti-myeloma treatment for patients with MM with concomitant cardiac diseases.

Methods: One hundred and forty-eight (males – 69, females – 79) patients were enrolled in this trial during March 2008 – May 2010. They divided on groups with (1) newly diagnosed and (2) relapsed and refractory MM. The median ages for patients of all groups was 64.7 years (ranges, 36.3 – 82.7). An obligatory condition was the presence in all patients of significant cardiac pathology. The bortezomib-containing regimens VCD (n = 95), VMP (n = 36) or VD (n = 15) were used as anti-myeloma treatment. IMWG (2006) criteria were used for anti-myeloma response assessment. Comparisons for categorical variables among different groups were wade with chi-square test. Overall survival (OS) was measured from the date of treatment initiation until the date of death or the date of last follow up. For multivariant analysis, factors associated with time to event were introduced into a Cox proportional model.

Results: ECOG performance status of ≤ 2 have 81 (54.7%) patients. The verified diagnosis of ischemic heart disease was in 109 (73.6%) patients and symptoms of chronic heart failure was in 86 (58.1%) patients. The overall response rate (ORR) documented in 65.7% cases with newly diagnosed and 59.5% cases with relapsed and refractory MM including complete and strong complete remission (CR/sCR) in 22.9% and 20.3% cases respectively. With a median follow-up of 4.9 years for the comparison groups, the 5-year overall survival (OS) was 22.8 $\pm$ 5.3% and 17.3 $\pm$ 4.4% (p = 0.295). The median OS was 40.0 and 31.8 months respectively.

Conclusions: In multivariate analysis only ECOG scores ≥ 2 were demonstrated an independent negative prognostic value both for the event-free survival (Hazard ratio 1.69; p = 0.006) and OS (Hazard ratio 1.76; p = 0.003). Overall, the bortezomib-based treatment in myeloma patients with concomitant cardiac pathology accompanied by no significant increase in the incidence of cardiovascular adverse events.

Legal entity responsible for the study: Pirogov Russian National Research Medical University (RNRMU) Research Medical University (RNRMU)

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1030P Evaluation of dose intensification of cytarabine in postremission therapy in older AML patients within the prospective phase II AMLSG 06-04 study

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Background: Progress in the treatment of acute myeloid leukemia (AML) in older patients (pts) is still limited. In the randomized part of the AMLSG 06-04 trial, valproic acid (VPA) was evaluated in combination with intensive therapy plus all-trans retinoic

acid (ATRA) in older pts (>60 years) with newly diagnosed AML. The randomized part of the study (cohort-1) was terminated due to excessive VPA-induced toxicity (Tassara et al, Blood 2014;123:4027-36.). The study was amended thereafter (cohort-2) to evaluate a cytarabine dose-intensifcation in first consolidation therapy. Here we report on the comparison of the two cohorts.

Methods: Between 2004 and 2008, patients were treated in cohort-1 (n = 186) and cohort-2 (n = 376). 2 cycles of induction therapy (ATRA, idarubicin, cytarabine, n = 93 with VPA) were followed by consolidation-1 (mitoxantrone, ATRA, cytarabine [cohort-1, 0.5g/m^2; cohort-2, 1g/m^2] bid, days 1-3) and consoldation-2 (idarubicin, etoposide, ATRA).

Results: Median age was 68 (range, 60-84) years without difference between the cohorts (p = 0.49). Complete remission (CR) rates after induction therapy were 45% and 48% (p = 0.59) in cohort-1 and -2, respectively. There were no significant differences in the cumulative incidences of relapse (CIR, p = 0.26) and death (p = 0.51) between cohort-1 and -2 with CIR of 63% (SE, 4.8%) in cohort-1 compared to 51% (SE, 6.3%) in cohort-2. A Cox regression model on overall survival revealed older age (hazard ratio (HR) for a 10 years difference, 1.97, p < 0.0001), 2010 European LeukemiaNet (ELN) unfavorable risk (HR, 1.57, p = 0.0003) as well as cohort-1 (HR, 1.31, p = 0.02) as unfavorable parameters and ELN favorable risk (HR 0.55, p < 0.0001) as favorable prognostic parameter. Survival was inferior (p = 0.03) in cohort-1 with 21% (95%-CI, 16-28%) compared to cohort-2 with 28% (95%-CI, 23-33%) at 2 years. In an age-adjusted analysis the molecular marker *FLT3*-ITD was associated with an unfavorable prognosis.

Conclusions: Although evaluated in a cohort- rather than a randomized study, intensification of cytarabine dosage in consolidation therapy seems to improve survival.

Clinical trial identification: NCT00151255

Legal entity responsible for the study: University Hospital Ulm

Funding: University Ulm, Pfizer

Disclosure: R. Schlenk: Research funding: Novartis, Pfizer, Amgen, AstraZeneca, PharmaMar; Speakers bureau: Novartis, Pfizer; Advisory board: Daiichi Sankyo, Novartis, Pfizer. All other authors have declared no conflicts of interest.

1031P The EUROSKI biomarker study: Analyzing the mechanisms of treatment-free remission in chronic myeloid leukemia

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Background: A substantial proportion of chronic myeloid leukemia (CML) patients in deep molecular response (DMR) reach treatment-free remission (TFR) after tyrosine kinase inhibitors (TKI) cessation. The aim of this study is to identify a gene signature predictive for TFR using whole transcriptome expression analyses.

Methods: RNA from peripheral blood (PB) leukocytes of 60 CML patients who stopped TKI therapy within the EUROSKI study and 10 healthy controls were isolated. CML patients were divided into two groups of whom n = 30 patients had ongoing TFR, while 30 patients encountered molecular recurrence. RNA was isolated at the last day of TKI intake. In order to investigate differentially expressed genes, whole transcriptome arrays (Clariom D, Affymetrix) were analyzed. Candidate biomarkers were tested in multivariate analyses and gene set enrichment analyses (GSEA).

Results: CML patients in DMR compared to healthy controls showed 16000 differentially expressed genes (p < 0.05). The natural killer cell marker *CD69* showed overexpression with highest fold change (> 8-fold) for CML patients versus healthy controls. Significant enrichment of NFκB mediated TNFα and TGFβ pathways (FDR<7%, p < 0.03) were found in CML patients. Comparing the CML TFR versus relapse cohort, we found 2600 differentially expressed genes. Most notably the toll-like receptors *TLR1*, *TLR6* and *TLR8* were upregulated in the relapse cohort (p < 0.03). Activated downstream signatures of NOD-like, TLR and TNFα pathways, known for their promotion of a protective CML microenvironment, were significantly enriched (p < 0.03, FDR<2%). In contrast, patients in TFR were characterized by an upregulation of T-cell receptor and granzyme gene family members (p < 0.03). Genes of interest showed distinct cut-offs predictive for TFR over a period of 12 months.

Conclusions: CML patients in DMR present a considerable inflammatory gene expression pattern in PB leukocytes in contrast to healthy controls. Alike previous studies, genes involved in immune exhaustion and immune surveillance were differentially expressed between patients with TFR and relapse. The specific inflammatory gene signature of the relapse cohort suggests 'stemness' as third mechanism and driver for relapse.

Legal entity responsible for the study: University Heidelberg

Funding: ELN Foundation

Disclosure: R. Sébastien: Novartis research fund. S. Saussele: Advisory board: Novartis, Bristol-Myers Squib, Pfizer and ARIAD Fees: Novartis, Bristol-Myers Squib, Pfizer and ARIAD Research grant: Novartis and Bristol-Myers Squib Travel grant: Novartis and Bristol-Myers Squib. All other authors have declared no conflicts of interest.

1032P Pharmacodynamic and pharmacokinetic evaluation of SY-1425 (tamibarotene) in biomarker-selected acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) patients

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Background: SY-1425 (tamibarotene) is an oral, potent and selective synthetic RARα agonist previously approved for the treatment of relapsed/refractory acute promyelocytic leukemia (APL) in Japan. Given preclinical evidence of SY-1425 sensitive AML cell lines and patient samples with RARA pathway activation defined by elevated RARA or IRF8, SY-1425 is being investigated in a Phase 2 study of biomarker selected non-APL AML and MDS patients. DHRS3 is a direct RARα target gene with rapid and robust mRNA upregulation in both AML blasts and PBMCs in response to SY-1425. Here we present the first report of SY-1425 plasma levels with DHRS3 based evidence of RARα target engagement from AML and MDS patients enrolled in the Phase 2 study (NCT02807558).

Methods: Patients positive for RARA pathway biomarkers (RARA, IRF8, or both) initiated oral daily treatment with SY-1425 at 6 mg/m2/day in two divided doses. Sparse PK was collected twice on day 1 and twice on day 15. PD was sampled before the first dose and at 5-8 hours post dose on day 1 and once on day 15. DHRS3 expression was assessed by qPCR in PBMCs.

Results: PK data in 16 patients showed SY-1425 plasma levels were consistent with those observed in Japanese APL patients based on day 1 Cmax and day 15 steady state exposure. In 19 PD evaluable patients, upregulation of DHRS3 at 5-8 hours had a greater than 2-fold increase in 84% (16/19). Induction was consistent for AML and MDS, including patients positive for RARA, IRF8, or both biomarkers. DHRS3 expression remained elevated after 15 days of continuous treatment in evaluable patients. Using a parallel exploratory *ex vivo* flow cytometry assay from screening samples, SY-1425 induced differentiation and blast reduction that was correlated with biomarker status.

Conclusions: In a biomarker-selected AML and MDS patients with evidence of RARA pathway activation, SY-1425 causes strong transcriptional upregulation of the DHRS3 target gene, consistent with SY-1425 induced differentiation through myeloid gene activation. The dosing regimen of SY-1425 achieves plasma exposures sufficient to elicit a PD response with direct evidence of RARα target engagement.

Clinical trial identification: NCT02807558 received by on June 13, 2016

Legal entity responsible for the study: Syros Pharmaceuticals

Funding: Syros Pharmaceuticals

Disclosure: J. Jurcic: Research funding from Syros Pharmaceuticals, Astellas Pharma, Daiichi Sankyo, Actinium Pharmaceuticals, Forma Therapeutics, Genetech, Seattle Genetics, Celgene, Kura Oncology. Advisor to Novartis. D. Rizzieri: Consultant for Abbvie, Novartis, Pfizer, Spectrum, Teva; speakers' bureau for Incyte, Celgene, Gilead, Seattle Genetics. J. Cortes: Research support from Syros Pharmaceuticals. R. Redner: Research funding from Bristol-Myers Squib; Stock or other ownership from Merk, Glaxo, JNJ, MDT, BIIB. G. Roboz: Advisory & funding: Agios, Astex, Celgene, CTI, MedImmune, MEI, Novartis, Onconova, Pfizer, Cellectis; funding: Abbvie, Karyopharm, Moffit, Tensha; Advisory:Amphivena, AstraZeneca, Boerhinger, GSK, Janssen, Roche, Shire, Amgen, Celator, Genoptix, Juno, Sunesis. M. McKeown, N. Waters, K. Stephens: Employee and stock holder of Syros. E. di Tomaso: Employee and stock holder from Syros Pharmaceuticals. D.A. Roth: Employee and stock holder of Syros Pharmaceuticals. E. Stein: Consulting for Agios, Pfizer, Celgene; research funding from Agios, Celgene, GSK, Seattle Genetics, Syros. All other authors have declared no conflicts of interest.

1033P Quantitative assessment of inotuzumab ozogamicin (InO) response relative to investigator's choice of chemotherapy (ICC) in adults with relapsed or refractory (R/R) CD22+ B-Cell acute lymphoblastic leukemia (ALL)

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Background: InO is a humanized CD22-targeted antibody conjugated to N-acetyl-γ-calicheamicin, a potent cytotoxic antibiotic. InO was administered to adult patients with R/R CD22+ B-cell ALL in a phase 1/2 (B1931010) study, and a phase 3 (INO-VATE) study that compared single-agent InO with ICC. The goal of this analysis was to quantify differences in response for the endpoints complete response (CR)/CR with incomplete hematologic recovery (CRi) and minimal residual disease-negativity (MRD (-)) for patients treated with InO relative to ICC.

Methods: The efficacy endpoints analyzed were CR/CRi per investigator's assessment and MRD (-). The modeling analyses were performed using generalized binomial logistic regression, which allows constructing a linear continuous predictor for probabilities of response ranging from 0%–100%. 2 treatment arms were considered: single agent InO or ICC (fludarabine, cytarabine, granulocyte colony-stimulating factor; cytarabine with mitoxantrone; or high-dose cytarabine). Additional potential predictors of response (eg, baseline demographic/patient characteristics, laboratory values) were also tested.

Results: For the CR/CRi efficacy endpoint, only 3 variables were statistically significant predictors of achieving CR/CRi: treatment arm, baseline ECOG (BECOG) performance status, and baseline absolute blasts in peripheral blood (BLSTABL). For the MRD (-) endpoint, 5 variables were statistically significant predictors of achieving MRD(-): treatment arm, BECOG performance status, baseline cytogenetic characteristics, prior hematopoietic stem cell transplant before study therapy, and BLSTABL.

Conclusions: The odds of achieving CR/CRi and MRD(-) with InO were approximately 7 and 13 times higher, respectively, than ICC.

Clinical trial identification: NCT01363297, NCT01564784

Legal entity responsible for the study: Pfizer Inc

Funding: Pfizer Inc

Disclosure: A. Ruiz-Garcia, E. Vandendries: Employee of and owns stocks in Pfizer Inc. D.J. DeAngelo: Served on advisory boards for Pfizer Inc. H.M. Kantarjian: Received research grants from Pfizer, Amgen, Astex, Novartis, and Bristol-Myers Squib. J. Boni: Was an employee of Pfizer Inc at the time the study was conducted.

1034TiP Phase III randomized, double-blind, controlled studies of the PI3K inhibitor copanlisib in combination with rituximab or rituximab-based chemotherapy in subjects with relapsed indolent B-cell non-Hodgkin's lymphoma (iNHL): CHRONOS-3 and CHRONOS-4

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Background: Copanlisib is a pan-Class I phosphatidylinositol 3-kinase (PI3K) inhibitor with predominant activity against PI3K-α and PI3K-δ isoforms. Recently, the CHRONOS-1 study demonstrated efficacy of copanlisib monotherapy in patients with relapsed or refractory iNHL with an acceptable safety profile (Dreyling et al., AACR 2017). Two randomized phase III studies are ongoing to evaluate the efficacy and safety of copanlisib in combination with standard therapy: Rituximab [R] either alone or in combination with chemotherapy including an alkylating agent (e.g. bendamustine [R-B] or CHOP [R-CHOP]) in $\geq 2^{nd}$ line iNHL patients who are relapsed but non-refractory to R or R-based chemotherapy.

Trial design: Both studies include iNHL patients (including follicular lymphoma, marginal zone lymphoma, small lymphocytic lymphoma, or lymphoplasmacytic lymphoma/Waldenström macroglobulinemia) who have relapsed but are non-refractory after at least 1 prior line of therapy including R. The primary efficacy variable is progression-free survival. In CHRONOS-3, 567 patients unfit/unwilling to receive chemotherapy or who have progressed or relapsed ≥12 months after the last R-based regimen will be randomized 2:1 to copanlisib (60 mg) or placebo administered intravenously on days 1, 8 and 15 of a 28-day cycle until progression in combination with 375 mg/m^2 of R days 1, 8, 15 and 22 followed by R bi-monthly up to cycle 9. For CHRONOS-4, a safety run-in phase will be conducted with 45 mg and 60 mg copanlisib with R-B or R-CHOP. Copanlisib will be admnistered (as above) with either B iv 90 mg/m2 days 1 and 2 each 28 days, or on days 1 and 8 of a 21-day cycle with CHOP per standard dosing. After the run-in phase, 520 patients eligible to receive R-B or R-CHOP will be randomized 1:1 to either copanlisib or placebo and receive up to 6 cycles followed by copanlisib or placebo monotherapy. Safety run-in of RB plus copanlisib was assessed by the Data Monitoring Committee and 60 mg was deemed as the copanlisib phase III dose (Gerecitano et al. ICML 2017). The phase III portion of the trial with copanlisib/placebo plus RB is ongoing.

Clinical trial identification: NCT02367040; NCT02626455

Legal entity responsible for the study: Bayer AG

Funding: Bayer AG

Disclosure: H. Zheng, R. Ito, C. Lu, J. Shen, B.H. Childs, L. Mongay Soler: Employment: Bayer HealthCare Pharmaceuticals Inc. D. Reis: Employment: Bayer SA. All other authors have declared no conflicts of interest.

1035TiP A multicenter, randomized, phase 3 study of pomalidomide and dexamethasone (Pom-dex) with or without daratumumab in patients with relapsed or refractory multiple myeloma (RRMM): APOLLO

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Background: Daratumumab (DARA), a human IgGκ monoclonal antibody targeting CD38, is approved in the United States and Europe for use in patients with RRMM, as a monotherapy and in combination with bortezomib/dexamethasone or lenalidomide/dexamethasone. In a phase 1b study, DARA plus pomalidomide and low-dose dexamethasone (Pom-dex) demonstrated efficacy and tolerability in patients with RRMM. Here, the safety and efficacy of DARA plus Pom-dex is evaluated in a phase 3 study.

Trial design: This is an ongoing, phase 3, multicenter, randomized, open-label study of DARA plus Pom-dex versus Pom-dex alone. Adults with RRMM who have received and responded to prior anti-myeloma therapy, including a proteasome inhibitor and a lenalidomide-containing regimen, and who have progressed on their last regimen are eligible. Patients who have received 1 prior line of therapy must have progressed ≤60 days of completing the lenalidomide-containing regimen. Patients will be randomized 1:1 to receive Pom 4 mg orally on Days 1-21 of a 28-day cycle plus dex 40 mg weekly (20 mg for patients ≥75 year of age), with or without intravenous DARA 16 mg/kg weekly in Cycles 1-2, every 2 weeks in Cycles 3-6, and monthly thereafter, until progression or unacceptable toxicity. To mitigate potential infusion-related reactions, all patients will receive pre-infusion medications (including dexamethasone, paracetamol,

Table: 1033P

Endpoint, n (%)	Category	Study B1931010 InO (n = 72)	INO-VATE InO Arm (n = 162)	INO-VATE ICC Arm (n = 143)	Total (N = 377)
MRD-negativity*	No	31 (43)	59 (36)	115 (80)	205 (54)
	Yes	41 (57)	97 (60)	23 (16)	161 (43)
	Missing	0 (0)	6 (4)	5 (3)	11 (3)
CR/CRi	No	23 (32)	42 (26)	95 (66)	160 (42)
	Yes	49 (68)	120 (74)	48 (34)	217 (58)

*When CR/CRi was not achieved and MRD was missing, MRD was considered not achieved.

diphenhydramine, and an optional leukotriene inhibitor) and patients with a higher risk of respiratory complications will receive post-infusion medications (including diphenhydramine, a short-acting β2 adrenergic receptor agonist, and lung disease control medications). Safety evaluations will occur weekly during Cycles 1-2, every other week during Cycles 3-6, and monthly thereafter. Disease evaluations will occur monthly. The primary endpoint is progression-free survival. Secondary endpoints include safety, overall response rate, minimal-residual-disease-negative rate, duration of response, and overall survival. Approximately 302 patients will be enrolled across 10 countries.

Clinical trial identification: Eudractnr: 2017-001618-27

Legal entity responsible for the study: Janssen Research & Development, LLC

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1036TiP Phase 2, multicenter, single-arm, open label study evaluating the combination of daratumumab + cyclophosphamide, bortezomib and dexamethasone (Dara-CyBorD) in previously untreated and relapsed patients (pts) with multiple myeloma (MM)

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Background: Dara is a monoclonal anti-CD38 antibody approved for the treatment of relapsed and refractory MM. Addition of dara to bortezomib and dexamethasone increased complete and overall response rates and improved progression-free survival (PFS) in pts with relapsed MM. CyBorD is a bortezomib based regimen which has been shown to be an effective therapy for MM. This study was designed to evaluate the combination of Dara-CyBorD in pts with MM who are previously untreated or have relapsed MM following only one line of prior therapy.

Trial design: This is a multicenter, single-arm, open label, Phase 2 study in pts with MM who have received ≤ 1 line of prior therapy. Approximately 100 pts (≥40 with untreated MM and ≥40 with relapsed MM) will receive Dara-CyBorD every 28 days for 4 to 8 cycles. Pts receive oral cyclophosphamide 300 mg/m2 on Days 1, 8, 15, and 22; subcutaneous bortezomib 1.5 mg/m2 on Days 1, 8, and 15; and oral or IV dexamethasone 40 mg weekly. Dara is administered concurrently on 28 day cycles at a dose of 8 mg/kg IV on Days 1 and 2 of Cycle 1, then 16 mg/kg IV weekly from Cycle 1 Day 8 through completion of Cycle 2. For Cycles 3-6, pts receive dara 16 mg/kg IV once every 2 weeks. From Cycle 7 onward, pts receive dara 16 mg/kg IV once every 4 weeks, whether with CyBorD or alone during the maintenance phase. Pts receive 4 to 8 induction cycles of Dara-CyBorD and eligible pts may undergo an autologous stem cell transplant. All eligible pts then receive 12 cycles of maintenance therapy with dara 16 mg/kg IV every 28 days. The primary endpoint is complete response (CR) plus very good partial response (CR+VGPR) following 4 cycles of induction therapy with Dara-CyBorD. Secondary endpoints include overall response rate (CR+VGPR+PR), time to VGPR and partial response, duration of response, PFS, overall survival rate, infusion reaction profile of split-dose infusions and safety. Inclusion criteria include ≥ 18 years of age; documented MM per IMWG 2015 criteria; an Eastern Cooperative Oncology Group performance status score of 0, 1, or 2; no or one prior line of therapy. The estimated primary endpoint analysis date is February 2018.

Clinical trial identification: NCT02951819

Legal entity responsible for the study: Janssen Scientific Affairs, LLC

Funding: Janssen Scientific Affairs, LLC

Disclosure: M. Sharma, L. Ey, H. Parros, S. Murphy, M. Darif, A. Londhe, J. Ukropec, M. Qi, Y. Lutska, T. Lin, S. Gunawardena: Author discloses employment with Janssen and Johnson & Johnson stock ownership.

1037TiP A double blind randomized phase 2 PILOT study of ERYASPASE in patients with acute lymphoblastic leukemia/lymphoma

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Background: Asparaginase is a critical agent in the treatment of ALL. This enzyme deaminates asparagine, interfering with protein synthesis and resulting in cell death as lymphoblasts are deficient in asparagine synthetase. Eryaspase is a dispersion of homologous red blood cells (RBCs) encapsulating L-asparaginase formulated in a preservative solution for infusion. The formulation of eryaspase has evolved during its development. Two sources of L-asparaginase (drug substance) from Medac GmbH can be used as raw material and encapsulated in the RBCs: native (Kidrolase®) or recombinant L-asparaginase (Spectrila®). This study is designed to investigate the PK comparability of both eryaspase formulations: native or recombinant asparaginase as the starting material, when administered as monotherapy and in combination with chemotherapy during induction and consolidation phases for the treatment of children and young adults presenting with ALL/LBL.

Trial design: This is a multicenter, multinational, double-blind, randomized, parallel group Phase 2 study of patients with de novo or relapsed ALL/LBL. After obtaining informed consent and performance of screening procedures, patients will be randomized to receive either eryaspase-N or eryaspase-R. Major Inclusion: Male or female, aged between 1-55 years Confirmed diagnosis of Philadelphia chromosome negative ALL/LBL, de novo or first relapse Adequate Performance Status Major Exclusion: Second intention asparaginase treatment in first-line setting. (These are patients who develop hypersensitivity reactions to another asparaginase and require switch to a different asparaginase formulation to complete the intended course of therapy) Refractory ALL/LBL (failure to achieve complete remission in first-line treatment) Recruitment will continue until 38 patients with a PK evaluable profile are enrolled.

Legal entity responsible for the study: Erytech Pharma

Funding: Erytech Pharma

Disclosure: N. Soule: Employed by Erytech Pharma. C. Holford, R. Kay: Consultant at Erytech Pharma. D. Tilton: Employed by Erytech Pharma. N. Biswas-Baldwin: Employee of Erytech Pharma. I. El Hariry: Employed by Erytech Pharma and have stock ownership.

1038TiP Phase 2 randomized study of daratumumab (dara), lenalidomide (R), bortezomib (V), and dexamethasone (d; Dara-RVd) vs. RVd in patients (pts) with newly diagnosed multiple myeloma (MM) eligible for high-dose therapy (HDT) and autologous stem cell transplantation (ASCT)

T. Lin[1], L. Hydutsky[2], H. Parros[3], S. Murphy[1], H. Pei[4], A. Londhe[4], J. Ukropec[5], M. Qi[6], Y. Lutska[1], M. Sharma[1]

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Background: Dara is an anti-CD38 antibody approved for the treatment of relapsed and refractory MM. Addition of dara to Vd and Rd improved complete (CR) and overall response (OR) rates and progression-free survival (PFS) in relapsed MM. RVd followed by HDT and ASCT achieves high response rates in previously untreated MM. The primary objective of this study is to determine if the addition of dara to RVd will increase the stringent CR (sCR) rate by the end of post-ASCT consolidation therapy.

Trial design: This is a multicenter, randomized, open-label, active-controlled study in newly diagnosed MM pts eligible for HDT and ASCT. Following a safety run-in for up to 16 pts to assess dose limiting toxicities, 200 additional pts will be randomized 1:1 to Dara-RVd or RVd. Pts receive 4 induction cycles of RVd +/- dara; followed by stem cell mobilization, HDT, and ASCT; 2 consolidation cycles of RVd +/- dara; and maintenance therapy with Rd +/- dara for 24 months. During induction and consolidation (cycles 1-6), all pts receive R 25 mg orally on Days 1-14; V 1.3 mg/m^2 subcutaneously on Days 1, 4, 8 and 11; and d 40 mg weekly; every 21 days. In the Dara-RVd group only, dara 16 mg/kg IV is given on Days 1, 8 and 15 of cycles 1-4 and on Day 1 of cycles 5-6. During maintenance, all pts receive R 10 mg daily on Days 1-21 every 28 days and d 20 mg every 56 days; dara 16 mg/kg IV is given every 56 days in the Dara-RVd group only. Inclusion criteria include age 18-70 years; eligibility for HDT and ASCT; documented MM; ECOG score of 0-2; adequate organ function; and no prior systemic therapy for MM. The primary endpoint is the sCR rate by the end of post-ASCT consolidation therapy. Secondary endpoints include rates of OR, CR, sCR, VGPR, and minimal residual disease negative status after induction, ASCT, consolidation and maintenance; time to initial response, VGPR, CR and sCR; duration of response; PFS; and overall survival. The study is being conducted at Alliance Foundation Trials (AFT) centers and other institutions in the US. The study has completed the 16 pt safety run-in phase and is currently enrolling pts in the randomized phase.

Clinical trial identification: NCT02874742

Legal entity responsible for the study: Janssen Research & Development, LLC

Funding: Janssen Research & Development, LLC

Disclosure: T. Lin, H. Parros, S. Murphy, H. Pei, A. Londhe, J. Ukropec, M. Qi, Y. Lutska, M. Sharma: Employment with Janssen and Johnson & Johnson stock ownership. L. Hydutsky: Employment with Janssen and Johnson & Johnson stock ownership.

1039TiP Phase 2a study of a novel stapled peptide ALRN-6924 disrupting MDMX- and MDM2-mediated inhibition of wild-type TP53 in patients with peripheral t-cell lymphoma

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Background: Peripheral T-cell lymphoma (PTCL) refers to a heterogeneous group of tumors that comprise a subset of T-cell non-Hodgkin lymphomas. PTCL-not otherwise specified, angioimmunoblastic T-cell lymphoma, and anaplastic large cell lymphoma are among the most common of these rare tumors. Outcomes are often poor, particularly in the setting of relapsed or refractory disease, making PTCL an ideal candidate for the assessment of a novel agent with strong biologic rationale. ALRN-6924 is a cell-penetrating stapled alpha-helical peptide designed to equipotently disrupt the interaction between the p53 tumor suppressor protein and its endogenous inhibitors, murine double minute X (MDMX) and 2 (MDM2). For TP53 wild-type (WT) tumors, pharmacological disruption of this interaction offers a means to induce p53-dependent cell cycle arrest and apoptosis, resulting in antitumor efficacy via a novel mechanism. ALRN-6924 demonstrated intriguing antitumor activity in a first-in-human phase 1 trial across a variety of tumor types (Meric-Bernstam et al., ASCO 2017, abstract #2505).

Trial design: This open-label Phase 2a study (NCT02264613) will enroll up to 20 adults with relapsed or refractory PTCL, after at least one prior systemic anticancer chemotherapy. Enrolled patients must have TP53 WT T-cell lymphoma (as confirmed by a central NGS testing), ECOG status of 0 or 1, and adequate organ function. Patients will receive 3.1 mg/kg ALRN-6924 as a one-hour infusion on days 1, 8, and 15 of 28-day cycles. Treatment will continue until disease progression or unacceptable toxicity. Response will be assessed according to the revised 2014 International Working Group (IWG) criteria for Lymphoma (Lugano Classification), (Cheson et al., J Clin Oncol. 2014:32:3059-3067). Primary objectives are to assess overall response rate and to further evaluate the safety and tolerability of ALRN-6924. Secondary objectives include assessment of time to response, duration of response, progression free survival, and overall survival. Pharmacodynamic biomarkers will be measured in blood and tumor samples. Recruitment is ongoing.

Clinical trial identification: NCT02264613

Legal entity responsible for the study: Aileron Therapeutics, Inc.

Funding: Aileron Therapeutics, Inc.

Disclosure: M. Payton: Employee of Aileron Therapeutics, including stock ownership. D. Pinchasik: Employee of Aileron Therapeutics, with equity. Stock ownership in Amgen. A. Mehta: Speaker bureau: Gilead Research Funding to Institution: Epizyme, Incyte, Genentech, Seattle Genetics, Bristol-Myers Squib, Merck. S. Goel: Patent "Method Of Determining The Sensitivity Of Cancer Cells To EGFR Inhibitors Including Cetuximab, Panitumumab And Erlotinib.", Patent No. 20090258364; Honoraria: Genentech/Roche; Research Funding: Oncolytics. J.M. Zain: Speaker's Bureau: Malickrodt, Spectrum, Seattle Genetics Advisory Boards: Celgene, Malickrodt, Spectrum, Seattle Genetics. M.R. Patel: Honoraria and Speaker's Bureau: Medivation, Bristol-Myers Squib, Exelixis, Genentech, Gilead Sciences. Consulting/Advisory Board: Guardant Health. S.M. Horwitz: Consulting/Research Funding: Celgene, Takeda, Kyowa-Hakka-Kirin, Seattle Genetics, Forty-Seven, Infinity Consulting: Huya Research: ADCT, Aileron, Spectrum. F. Meric-Bernstam: Honoraria: Genentech, Roche; Consult: Genentech, Novartis, Roche, Inflection, Celgene, Pieris, Clearlight; Funding: Novartis, AstraZeneca, Taiho, Genentech, Calithera, Debiopharm, Bayer, Aileron, Puma, Verastem, CytomX, Jounce, Zymeworks, Effective, Curis. D. Weinstock: Research Funding: Aileron Therapeutics. M. Aivado, D.A. Annis: Employee of Aileron Therapeutics, with equity. All other authors have declared no conflicts of interest.

1040TiP QuANTUM-First: phase 3, double-blind, placebo-controlled study of quizartinib in combination with induction and consolidation chemotherapy, and as maintenance therapy in patients (pts) with newly diagnosed (NDx) FLT3-ITD acute myeloid leukemia (AML)

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Background: FLT3-internal tandem duplication (ITD) mutations occur in ∼25% of NDx AML pts and are associated with shorter response duration to standard chemotherapy (SC), higher relapse rate, and lower overall survival (OS) vs non–FLT3-ITD AML. Unlike the multi-kinase inhibitor, midostaurin, Quizartinib (Q), an oral, highly potent FLT3 inhibitor, has greater selectivity for FLT3. Early clinical studies of Q combined with SC demonstrated high clinical activity in NDx FLT3-ITD AML pts. This is an ongoing phase 3 trial of Q vs placebo (P) added to induction (IND) and consolidation (CON) chemotherapy and as maintenance therapy in NDx FLT3-ITD AML pts.

Trial design: Pts age 18-75 years with NDx *FLT3*-ITD AML and ECOG PS 0-2 are eligible. Key exclusion criteria: any prior treatment (including Q or any FLT3 inhibitors), investigational drug or device $\leq$30 days (d), immunotherapy $\leq$2 weeks, history of central nervous system leukemia, significant cardiovascular disease, QTcF >450 msec, active liver disease. Pts are randomized 1:1 to Q 40 mg (equivalent to 35.4 mg free base) or P administered with IND and CON chemotherapy ($\leq$4 cycles high-dose cytarabine $\pm$ hematopoietic stem cell transplant) then as maintenance (Q 30 mg titrated to 60 mg, $\leq$12 28-d cycles; or P). In IND cycle 1, pts receive cytarabine 100 (or 200 mg/m^2/d per updated protocol) for 7 d + anthracycline (daunorubicin 60 mg/m^2/d or idarubicin 12 mg/m^2/d) on days 1-3 (7 + 3). Starting day 8 of each IND and day 6 of each CON cycle, pts receive 14 d of daily Q 40 mg or P. On the second IND cycle, pts receive the 7 + 3 protocol, or investigators may substitute 5 + 2 d of cytarabine and anthracycline, per institutional standards, with Q or P starting on day 8 or day 6, respectively. The primary endpoint is event-free survival based on centrally adjudicated response assessment using local morphology results. Secondary endpoints are OS, CR, CRc (CR + CRi per latest IWG definitions). Enrollment is underway at 167 sites with a target enrollment of 536 pts at 275 sites worldwide.

Clinical trial identification: NCT02668653 First Received/Release date: January 22, 2016

Legal entity responsible for the study: Daiichi Sankyo, Inc.

Funding: Daiichi Sankyo, Inc.

Disclosure: R. Schlenk: Reports grants and personal fees from Novartis, grants from Amgen, grants and personal fees from Pfizer, grants from AstraZenca, grants from PharmaMar. H. Dombret: Grants and personal fees- Pfizer, Incyte, Jazz Pharma, Kite Pharma, Amgen; personal fees- Novartis, Celgene, Agios, Sunesis, Daiichi Sankyo, Karyopharm, Menarini, Astellas, Janssen, Servier, Seattle Genetics, Cellectis. S. Amadori: Reports personal fees from Novartis, personal fees from Amgen, personal fees from Celgene. P. Montesinos: Reports research funding: Pfizer, Celgene and advisory board: Daiichi Sankyo, Novartis, Pfizer, Celgene. M. Levis: Reports personal fees from Daiichi-Sankyo. M.A. Sekeres: Celgene and Millennium, advisory Boards, and steering committee for Daichii-Sankyo. J. Cortes: Grants and personal fees from Ambit/Daiichi, during the conduct of the study; grants and personal fees from Astellas, grants and personal fees from Ariad, grants from Arog, grants and personal fees from Novartis. A. Perl: personal fees and non-financial support- Daiichi Sankyo, Novartis, Arog Pharmaceuticals, personal fees from Pfizer, Astellas, Asana biosciences. O. Zernovak, S. Macintyre, S. Gökmen, K. Kobayashi, D. Mires, H. Zhang, J. Hanyok, N. Ge: Employee of Daiichi Sankyo, Inc. H. Erba: Personal fees- Celgene, Incyte, Novartis, Amgen, Jazz, Daiichi, ImmunoGen, Millennium/Takeda, Ono, Pfizer, Seattle Gen, Sunesis, Glycomimetics; grants- Agios, Amgen, Astellas, grants-Celator, Daiichi, ImmunoGen, Janssen, Juno, Millennium/Takeda, Seattle Gen

1041TiP MP0250 – a dual inhibitor of VEGF and HGF - plus bortezomib + dexamethasone in a phase 2 open-label, single-arm, multicenter trial in patients with refractory and relapsed multiple myeloma (RRMM)

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Background: Despite recent advances in the treatment of multiple myeloma (MM), patients eventually relapse, requiring multiple lines of treatment. Upregulation of both the vascular endothelial growth factor (VEGF) and hepatocyte growth factor (HGF) pathways has been implicated in loss of response to therapy and linked to poor prognosis through different mechanisms such as stimulation of angiogenesis, bone destruction, and myeloma cell proliferation and migration. MP0250 is a first-in-class, trispecific multi-DARPin® drug candidate neutralizing VEGF and HGF as well as binding to human serum albumin to increase plasma half-life. MP0250 shows activity in multiple preclinical tumor models amongst them an MM model in which it enhances the effects of bortezomib on e.g. M protein production and bone lysis. MP0250 has shown a favorable safety profile in a Phase 1 clinical trial in advanced solid tumors.

Trial design: This trial is recruiting adults ≥18 years of age with RRMM who have received ≥2 lines of therapy (including bortezomib and an immunomodulatory drug [IMiD]), have not shown any response to and have progressed on or within 60 days of the most recent treatment. The primary endpoint is efficacy in terms of overall response rate (ORR). Secondary endpoints include safety and immunogenicity. A total of 40 patients will be enrolled, 12 patients during a lead-in phase (Part 1) to establish a safe dose and an additional 28 patients in Part 2 to make a total of 34 patients at the target dose. Patients will receive study treatments (MP0250 in combination with bortezomib + dexamethasone) until the end of the study, disease progression, unacceptable toxicity, or other criteria for discontinuation, whichever occurs earlier. Cytogenetic analyses, response assessment, exploratory biomarkers, pharmacokinetics and immunogenicity will be determined in either bone marrow and/or blood/urine. The trial is currently recruiting patients.

Clinical trial identification: EUDRACT number: 2016-002771-10

Legal entity responsible for the study: Molecular Partners AG

Funding: Molecular Partners AG

Disclosure: M.S. Raab, R. Ria, J. Schlenzka, A. Vacca, H. Goldschmidt: Has been involved in design of the trial and received study funds through the university for performing the Trial. T. Krahnke: TK has been involved in statistical design of the trial and received consultancy funds. J. Haunschild, F. Herrmann, U. Fiedler, K. Dawson: JH is a full-time employee of Molecular Partners AG. M.T. Stumpp, A. Harstrick: CSO of Molecular Partners AG. K. Tadjalli Mehr: Medical consultant to Molecular Partners AG.

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HEAD AND NECK CANCER, EXCLUDING THYROID

1042O Durvalumab for recurrent/metastatic (R/M) head and neck squamous cell carcinoma (HNSCC): Preliminary results from a single-arm, phase 2 study

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Background: R/M HNSCC patients (pts) who have progressed on platinum-based chemotherapy have a poor prognosis and limited therapeutic options. Programmed cell death 1 (PD-1) and its ligand 1 (PD-L1) are frequently up-regulated in several tumor types, including HNSCC. The global, single-arm, Phase 2 HAWK study (NCT02207530) evaluated the anti-PD-L1 immunotherapy durvalumab as monotherapy in PD-L1 high pts with R/M HNSCC who have failed platinum-based chemotherapy.

Methods: Immunotherapy-naïve pts aged ≥18 years with confirmed PD-L1 high protein expression (≥25% of tumor cells [TCs] using the Ventana SP263 assay) who had progression or recurrence during/after 1 platinum-based regimen for R/M HNSCC received durvalumab 10 mg/kg IV every 2 weeks up to 12 months or until progression, starting another anticancer therapy, consent withdrawal, or unacceptable toxicity. The primary endpoint was objective response rate (ORR; blinded independent central review, RECIST v1.1); secondary endpoints included progression-free survival (PFS) and overall survival (OS).

Results: As of Sept 26, 2016, 112 pts from 12 countries had received treatment (median age 60 years, 71.4% male, 34.7% human papillomavirus [HPV]+, and 61.6% current/former smokers). Median durations of treatment and follow-up were 3.45 and 5.96 months, respectively. Among evaluable pts (n = 111), ORR was 13.5% (95% CI 7.8−21.3) overall and 26.5% (95% CI 12.9−44.4) and 7.9% (95% CI 2.6−17.6) for HPV+ and HPV- pts, respectively; among responders (n = 15), 12 (80%) had an ongoing response at data cutoff (DCO). 35 pts (31.5%) had stable disease ≥8 weeks. Median PFS was 2.3 months (95% CI 1.9−3.7) and 34 pts (30.4%) were alive at DCO (OS data were immature). The incidence of grade ≥3 treatment-related adverse events (AEs) was 9.8% and no treatment-related AEs led to death. 88 pts (78.6%) discontinued initial study treatment, 65 (58%) due to progressive disease and 10 (8.9%) due to all-causality AEs.

Conclusions: Durvalumab demonstrated promising antitumor activity with an acceptable safety profile in PD-L1 high pts with R/M HNSCC, supporting its potential use, and the opportunity to improve efficacy, in combination therapy.

Clinical trial identification: NCT02207530 (release date: August 1, 2014)

Legal entity responsible for the study: AstraZeneca PLC

Funding: AstraZeneca PLC

Disclosure: D. Zandberg: PI at UMGCCC for trials by Medimmune, AstraZeneca, Merck, Macrogenics, Bristol-Myers Squib, Gliknik. A. Algazi: UCSF receive research funding on my behalf from AstraZeneca, Merck, Bristol-Myers Squib, MedImmune, Acerta, OncoSec, Novartis. A. Jimeno: Consultant for AstraZeneca, one presentation at research meeting in January 2016 J.S. Good: Corporate sponsored research: AstraZeneca and Honoraria: Eisai, Bayer, Sirtex, BTG J. Fayette: Honoraria: Bristol-Myers Squib, AstraZeneca. N. Ready: Consultant: AstraZeneca, Bristol-Myers Squib, Merck, Celgene, Abbvie and Honoraria: Bristol-Myers Squib, Abbvie. P.M. Clement: Speakers' Bureau and Corporate sponsored research: AstraZeneca. T. Goswmi, A. Jarkowski, J.M. Armstrong: Employee & Shareholder of AstraZeneca. K. Asubonteng: Employee & Shareholder of AstraZeneca. Corporate sponsored research: AstraZeneca. G. Melillo: Employee & Shareholder of AstraZeneca. R. Mesía: Speakers' Bureau: Merck, SL and Consultant: Merck, SL, MSD, Bayer, AstraZeneca, Bristol. All other authors have declared no conflicts of interest.

1043O Treatment beyond progression with nivolumab in patients with recurrent or metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN) in the phase 3 checkmate 141 study: A biomarker analysis and updated clinical outcomes

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Background: Treatment responses to immune checkpoint inhibitors may occur after initial radiologic evidence of progression. In CheckMate 141 (NCT02105636), a randomized phase 3 study in patients (pts) with R/M SCCHN, nivolumab (nivo) significantly prolonged overall survival (OS) vs single-agent of investigator's choice (HR = 0.70 [97.73% CI: 0.51, 0.96]). We provide a biomarker analysis and updated clinical outcomes of nivolumab treatment beyond first disease progression.

Methods: This analysis is based on a Sept 2016 database lock (minimum follow-up: 11.4 mo). Progression was assessed per RECIST 1.1. Treatment beyond first progression was permitted in the nivo arm for pts who met protocol defined criteria. Pts without progression or tumor assessment to determine progression were excluded. Immune cell phenotyping was conducted by flow cytometry for pts with samples available for both day 1 (D1) and D43 of treatment, and associated with clinical response status.

Results: Of 240 pts randomized to nivo, 146 (61%) experienced progression. Among them, 62 (42%) received ≥1 dose of nivo after progression (TBP group), and 84 (58%) were not treated beyond progression (NTBP group). Median OS was 12.7 mo (95% CI: 9.7, 14.6) in the TBP group. After initial progression, 15 (24%) pts in the TBP group had a reduction in target lesion size, with >30% reduction in 3 pts. Of these 15 pts, 8 were HPV+, 4 had PD-L1 ≥1%, and 5 had >20% increase in target lesion at first progression. Frequencies of grade 3−4 treatment-related adverse events were similar in the TBP and NTBP groups. At D1 and D43, the percentage of CD8+ T cells in peripheral blood for TBP pts (n = 5) was similar to that for responders (n = 15), which was significantly higher vs NTBP pts (n = 9). At D1, the percentage of PD-1+ CD8+ effector T cells was significantly lower in responders and TBP pts vs NTBP pts. At D1, TBP pts, similar to responders, had a significantly lower PD-1+ Treg percentage vs NTBP pts.

Conclusions: Nivo treatment beyond progression in some pts with R/M SCCHN was tolerable and associated with tumor size reductions. Certain immune cell profiles in the TBP group appear similar to those of responders.

Clinical trial identification: NCT02105636

Legal entity responsible for the study: Bristol-Myers Squibb

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1044O Long-Term Safety and Clinical Outcomes of Atezolizumab in Head and Neck Cancer: Phase Ia Trial Results

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Background: Checkpoint inhibitors have shown efficacy in pts with recurrent and/or metastatic head and neck cancer (HNC). Atezolizumab (atezo; anti—PD-L1) inhibits binding of PD-L1 to PD-1 and B7.1, thereby restoring tumor-specific T-cell immunity. Here, we examine single-agent safety and clinical activity of atezo in pts with advanced HNC.

Methods: Pts with HNC received atezo IV q3w (15 or 20 mg/kg or 1200 mg) in a Ph Ia study (NCT01375842). Pts were initially enrolled non-selectively (n = 10); once PD-L1 was identified as a potential biomarker, pts were selected by PD-L1 status (> 5% PD-L1 expression on IC [IC2/3]; centrally evaluated by VENTANA SP142 IHC assay, n = 22). HPV status was assessed by PCR. Treatment was originally for 16 cycles or up to 1 y; pts were subsequently treated until loss of clinical benefit. Primary endpoint was safety; tumor responses were evaluated by RECIST v1.1.

Results: As of 31 Dec 2016, with follow-up of ≥ 14 mo, 32 pts were safety and efficacy evaluable. 84% were male; 66% had ECOG PS of 1. Median age was 62 y (range, 32-78 y), pts were heavily pre-treated (53% had ≥ 2 prior lines of therapy) and 66% were current/previous tobacco users. Most common primary tumor sites were oropharynx (50%), oral cavity (22%) and nasopharynx (19%). Median treatment duration was 3.4 mo; 21/32 pts (66%) had a treatment-related AE. 3 pts (9%) had Gr 3 treatment-related AEs (tumor lysis syndrome, hyponatremia, pruritus, colitis). 1 pt (3%) had Gr 4 treatment-related cardiac tamponade. No Gr 5 treatment-related AEs were seen. In all pts (IC0/1, n = 7; IC2/3, n = 25), confirmed ORR was 22%, mPFS was 2.6 mo (range, 0.5-48.4 mo) and mOS was 6.0 mo (range, 0.5-51.6+ mo). Clinical activity by PD-L1 subgroups is shown in the Table. Preliminary analyses indicate that there was no association between HPV status and clinical outcomes.

Conclusions: In advanced HNC, atezo was well tolerated. Encouraging response and long-term survival were seen independently of PD-L1 IHC or HPV status and warrant further investigation.

Table: 1044O Clinical Activity per RECIST v1.1 in PD-L1 Subgroups

	IC0/1[a] (n = 7)	IC2/3[a] (n = 25)
ORR, n (%)	1 (14%)	6 (24%)
CR	0	0
PR	1 (14%)	6 (24%)
DCR, n (%)	3 (43%)	7 (28%)
mDOR, mo (range)[b]	7.4	26.2 (2.8-45.8)
mPFS, mo (range)	5.7 (0.5-13.5)	2.6 (0.5-48.4)
mOS, mo (range)	9.0 (0.5-26.5)	5.6 (1.1-51.6+)
1-year OS rate	43%	34%
2-year OS rate	29%	18%
3-year OS rate	NE	18%

[+]indicates a censored value.

[a]Data by PD-L1 expression on TC will be presented.

[b]n = 1 for IC0/1, no estimate for mDOR; n = 6 for IC2/3.

IC0 = PD-L1 expression on < 1%; IC1 = ≥ 1% to < 5%; IC2 = ≥ 5% to < 10%; IC3 = ≥ 10%.

PD-L1 subgroups do not reflect the natural prevalence as not enrolled as an all-comer cohort.

DCR, disease control rate: % of pts with CR, PR and SD ≥ 24 wk;

IC, tumor-infiltrating immune cells; mDOR, median duration of response; TC, tumor cells.

Clinical trial identification: NCT01375842

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

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1045PD Adjuvant androgen deprivation therapy for high-risk androgen receptor-positive salivary duct carcinoma

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Background: Salivary duct carcinoma (SDC) is a rare and aggressive subtype of salivary gland cancer, with a median disease-free survival (DFS) of less than 3 years. SDC is androgen receptor-positive (AR+) in 67-96% of cases. In incurable recurrent AR+ SDC androgen deprivation therapy (ADT) has an overall response rate of 18-50%. In this study, high-risk AR+ SDC pts were treated with adjuvant ADT to study the efficacy.

Methods: In this retrospective study, surgical resected pts who received adjuvant ADT for stage 4a/b AR+ SDC at the Radboudumc (Nijmegen, the Netherlands) or Istituto Nazionale dei Tumori (Milan, Italy) were collected. As control group, surgical resected pts diagnosed with stage 4a/b SDC between 1990-2014, who did not receive adjuvant ADT were collected by a search of the Dutch pathology database (PALGA). Pts were analyzed for DFS and overall survival (OS) by using Kaplan-Meier survival curves.

Results: 18 AR+ SDC pts (median age 64 years [range 32-80]) were treated with adjuvant ADT (Nijmegen n = 11; Milan n = 7) for a median duration of 10 months [range 2-31 months]. All pts had a nuclear AR-staining pattern in > 70% of the cells. They were treated with bicalutamide monotherapy (n = 10), a LHRH analog (n = 1) or a combination of these (n = 7). Treatment was well tolerated. 17/18 pts (94.4%) also received postoperative radiotherapy, of which 4 pts received concurrent chemoradiotherapy (22.2%). The control group consisted of 110 SDC pts (median age 70 years [range 44-100]). 103/110 pts (93.6%) received postoperative radiotherapy, of which 1 pt received concurrent chemoradiotherapy (0.9%). After a median follow-up of 22 months in the ADT-treated SDC pts and 25 months in the control SDC pts, the 3-year DFS was 53.6% and 34.2% (p = 0.137), the 3-year OS was 68.2% and 52.3% (p = 0.198), respectively. The median DFS and OS were not reached in the ADT-treated SDC pts and were 21 months and 46 months in the control SDC pts.

Conclusions: Adjuvant ADT in high-risk AR+ SDC pts did not lead to a significant increase in DFS or OS, but the number of treated pts was limited. Due to the rarity of the disease we could not perform a formal phase II study. Translational research to identify pts which may benefit from ADT is warranted.

Legal entity responsible for the study: Carla M.L. van Herpen

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Disclosure: All authors have declared no conflicts of interest.

1046PD Overexpression of the c-MET proto-oncogene in salivary duct carcinoma patients

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Background: Salivary duct carcinoma (SDC) is a rare and aggressive subtype of salivary gland cancer (SGC). Activation of the cellular MET (c-MET) receptor tyrosine kinase has been implicated in cell proliferation, survival, migration, and invasion. The aim of this study was to evaluate the frequency of MET overexpression and its correlation to clinicopathological factors in SDC.

Methods: 136 patients were collected by a retrospective search of the Nationwide Network and Registry of Histo- and Cytopathology (PALGA) in the Netherlands. Formalin-fixed paraffin-embedded tumor blocks and hematoxylin and eosin stained slides were requested for pathological review. MET expression was evaluated by immunohistochemical staining on primary tumors. These data were correlated to clinicopathological factors.

Results: c-MET was positive in 54 of 136 tumors (39.7%). Of these 54 tumors, 50 had a cytoplasmic staining pattern and 23 had a membranous staining pattern, so in 19 tumors both cytoplasmic and membranous staining was observed. No correlations were found between cytoplasmic or membranous MET and high stage disease (stage 3 and 4 versus stage 1 and 2, $p = 0.606$ and $p = 0.300$ respectively), number of positive lymph nodes ($p = 0.263$ and $p = 0.955$ respectively), lymph node ratio ($p = 0.192$ and $p = 0.771$ respectively), androgen receptor-status ($p = 0.858$ and $p = 0.258$ respectively), HER2-status ($p = 0.257$ and $p = 0.595$ respectively), time to recurrence ($p = 0.559$ and $p = 0.959$ respectively), time to distant metastases ($p = 0.398$ and $p = 0.666$ respectively), or overall survival ($p = 0.754$ and $p = 0.516$ respectively). Membranous MET staining occurred more frequently in SDC ex pleomorphic adenoma (14 of 52 tumors) than in the '*de novo*' SDC (9 of 84 tumors) ($p = 0.014$). In SDC ex pleomorphic adenoma we also found more HER2-positive tumors ($p = 0.041$).

Conclusions: Cytoplasmic and membranous MET are overexpressed in SDC and may be a target for MET-targeted therapy. It is not a prognostic factor for overall survival, possibly because frankly invasive SGCs often show less receptor expression then minimally invasive SGCs or pleomorphic adenomas. The higher expression of c-MET and HER-2 in SDC ex pleomorphic adenoma needs further investigation.

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Disclosure: All authors have declared no conflicts of interest.

1047PD Mammary analogue secretory carcinoma (MASC): clinical characteristics in 28 ETV6-NTRK3 fusion gene confirmed patients

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Background: Recently, a new subtype of salivary gland cancer (SGC), mammary analogue secretory carcinoma (MASC), has been defined, which is characterized by the presence of ETV6-NTRK3 fusion gene. Previously, MASC was mixed up with acinic cell carcinoma (AciCC), polymorphous low grade adenocarcinoma and (cyst)adenocarcinoma. At present the clinical features and outcome of MASC patients are not well known. We aimed to describe the clinical presentation and outcome of MASC.

Methods: Firstly, we re-evaluated the pathological diagnosis of salivary gland cancers with a morphological resemblance to MASC, diagnosed in 4 of the 8 head and neck centres in the Netherlands, for their presence of ETV6-NTRK3 and also included genetically confirmed prospectively diagnosed cases. The ETV6-NTRK3 fusion gene was analyzed using RT-PCR. Secondly, the clinical characteristics were retrieved from the patient files.

Results: Twenty-eight patients with ETV6-NTRK3 fusion gene positive MASC were included (10 prospectively and 18 retrospectively). Of these 18 retrospective patients 13 patients were previously diagnosed as AciCC, the other 5 patients as (low-grade) adenocarcinoma. The median age at diagnosis was 49 years (range 19 – 83 years), 15 patients (54%) were male. The duration of symptoms varied from 6 weeks until 20 years with a median of 14 months. In 18 patients (64%) the tumour was located in the parotid gland; the other patients had tumours of the minor salivary glands (2), submandibular gland (1), oral mucosa/lip (5) or palate (2). All patients had a T1-2 tumour. One patient had lymph node metastasis at diagnosis. All patients underwent surgery of which 4 patients needed re-resection and 12 patients (43%) underwent postoperative radiotherapy. One patient had a local recurrence 50 months after primary surgery, but was cured after second resection. None of the patients had regional recurrences or distant metastases. The median follow-up was 49 months and both the 5- and 10-year overall survival rate were 94%.

Conclusions: MASC is a recently acknowledged new entity of SGC characterized by the ETV6-NTRK3 fusion gene. The clinical course seems to be favourable with a very low rate of recurrences and an excellent survival.

Legal entity responsible for the study: Radboudumc

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1048PD RetroSpective cohort stUdy of PD-L1 expression in REcurrent and/or MEtastatic squamous cell carcinoma of the head and neck (SUPREME-HN)

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Background: Clinically meaningful antitumour activity and improved overall survival (OS) in recurrent and/or metastatic (R/M) head and neck squamous cell carcinoma (HNSCC) have been achieved by targeting the PD-1/PD-L1 axis. Tumoral PD-L1 expression correlates with response to blocking PD-1/PD-L1 antibodies. In a retrospective study, we investigated tumoral PD-L1 expression as a prognostic biomarker in R/M HNSCC patients (pts) treated with standard of care (SOC) therapy.

Methods: Archival tumor samples from R/M HNSCC pts diagnosed between March 2011 and June 2015 at 19 institutions in 7 countries were evaluated for PD-L1 expression using the validated Ventana SP263 assay and scored as PD-L1 high ($\geq$25% of tumor cells [TC]) or low/negative (<25% of TC). Clinical-demographic data, including treatment patterns and outcomes, were extracted from medical records. Descriptive analyses were conducted and survival estimated by the Kaplan-Meier method. Progression-free survival (PFS) was defined from start of first- (1L) or second-line (2L) therapy to time of progression (on/after therapy) or death due to any cause. OS was defined from diagnosis index date of R/M disease to time of death. The Cox proportional hazards model was applied.

Results: The final dataset included 412 pts. Median age was 62.0 years (range 28.0–93.0); 79.9% were male and 88.2% white. PD-L1 expression was high in 132 (32.0%), low/negative in 264 (64.1%), unknown in 16 (3.9%). Median OS (8.2 vs 10.1 months; $P = 0.55$) and PFS from the start of 1L chemotherapy (4.2 vs 4.8 months; $P = 0.37$) did not significantly differ between PD-L1 high and low/negative pts, respectively. Median PFS following 2L chemotherapy was statistically significantly longer in PD-L1 high versus low/negative pts (4.1 vs 2.2 months; $P = 0.04$). PD-L1 status was not statistically significant in multivariate analyses of OS ($P = 0.74$) or PFS following 1L chemotherapy ($P = 0.63$); however, there was a trend for improved PFS following 2L chemotherapy ($P = 0.09$).

Conclusions: Tumoral PD-L1 expression was not significantly associated with OS or PFS following 1L SOC chemotherapy; however, it was associated with prolonged PFS following 2L SOC chemotherapy.

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1049PD Relationship between PD-L1 expression and survival in head and neck squamous cell carcinoma (HNSCC) patients (pts)

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Background: Programmed cell death 1 (PD-1) and its ligand 1 (PD-L1) are up-regulated in many cancers. The purpose of this study was to explore the relationship between PD-L1 expression and overall survival (OS) in HNSCC.

Methods: A retrospective study was conducted using data from pt medical records and analysis of archival tumor samples. Sample ages ranged from 8.2 to 227.5 months. Pts $\geq$18 years old diagnosed with HNSCC between 1989 and 2015 were selected. Demographic and tumor characteristics were compared by PD-L1 expression status. PD-L1 testing was performed using the Ventana PD-L1 SP263 assay. PD-L1 expression was scored separately using tumor cell (TC) and immune cell (IC) membrane staining and exploratory cut-offs of 1%, 5%, 10%, 25% and 50%. OS was calculated as the number of months from initial HNSCC diagnosis until death and estimated using the Kaplan–Meier method. The log-rank test was used to compare survival curves by PD-L1 status. PD-L1 status as a prognostic indicator of OS was further examined in Cox proportional hazards (PH) models.

Results: We identified 214 HNSCC pts with data available for date of death/last follow-up and PD-L1 status. Mean (SD) tumor sample age was 93.3 (40.5) months. Mean (SD) pt age was 62.3 (13.4) years and 70% were male. The Table presents baseline characteristics by PD-L1 subgroup. Median OS was similar between PD-L1 high and low/negative pts classified using the TC $\geq$ 25%, IC $\geq$ 1%, and IC $\geq$ 25% cut-offs. However, median OS was 21.2 months longer in PD-L1 high versus low/negative pts (68.9 vs. 47.7 months, respectively; P=0.03) in analyses using the TC $\geq$ 1% cut-off. This latter relationship remained after adjusting for baseline covariates using Cox PH models.

Conclusions: PD-L1 high expression based on a TC $\geq$ 1% cut-off appears to be associated with improved OS in this sample of pts with HNSCC. A small number of samples and resulting low statistical power limited our ability to assess prognosis for TC $\geq$ 25% and IC $\geq$ 25%, yet OS was numerically higher among PD-L1 high pts in these subgroups.

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1050PD The ELAN-ONCOVAL (ELderly heAd and Neck cancer-Oncology eValuation) study: Evaluation of the feasibility of a suited geriatric assessment for use by oncologists to classify patients as fit or unfit

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Background: About 47% and 10% of head and neck squamous cell carcinomas (HNSCC) occur in patients (pts) aged 65+ or 80+ respectively. This population being heterogeneous, balancing efficacy with toxicity is challenging.

Methods: ONCOVAL is the first step of the ELAN program for pts 70+ with HNSCC, not amenable to surgery. During ONCOVAL, pts were assessed for frailty before inclusion to appropriate trial depending on curative or palliative setting and fit or unfit status. The primary aim was to evaluate whether a suited geriatric evaluation (SGE) for use by oncologist is feasible to stratify pts as fit or unfit. The SGE was elaborated by GERICO (French UNICANCER group dedicated to clinical research in elderly cancer pts) specifically for HNSCC pts, derived from the comprehensive geriatric assessment (CGA) and evaluating functional status, comorbidity, cognition, mental health status, social status, nutrition. Full CGA performed by geriatricians was optional.

Table: 1049PD Baseline characteristics

Characteristic	TC PD-L1 expression			
	High (≥25%)	Low/negative (<25%)	High (≥1%)	Low/negative (<1%)
No. of pts (%)	33 (15.4)	181 (84.6)	118 (55.1)	96 (44.9)
Mean (SD) age, years	57.3 (12.3)	63.2 (13.4)	61.1 (12.9)	63.8 (13.8)
HPV positive, %	42.4	45.3	45.8	43.8
Present smoker, %	24.2	36.5	31.4	38.5
Stage IV, %	33.3	51.4	48.3	49.0
African American, %	27.3	16.6	22.9	12.5
Median OS, months	Not reached	62.9	68.9	47.7
p-value*	0.27		0.03	
	IC PD-L1 expression			
	High (≥25%)	Low/negative (<25%)	High (≥1%)	Low/negative (<1%)
No. of pts (%)	11 (5.1)	203 (94.9)	150 (70.0)	64 (30.0)
Mean (SD) age, years	63.8 (10.1)	62.2 (13.6)	61.3 (13.4)	64.6 (13.2)
HPV positive, %	8 (72.7)	88 (43.4)	75 (50.0)	21 (32.8)
Present smoker, %	3 (27.3)	71 (35.0)	53 (35.3)	21 (32.8)
Stage IV, %	6 (54.5)	98 (48.3)	68 (45.3)	36 (56.3)
African American, %	4 (36.4)	35 (17.2)	31 (20.7)	8 (12.5)
Median OS, months	157.1	68.9	79.0	52.5
p-value*	0.31		0.07	

*log-rank p-value comparing high vs. low/negative groups

Results: Between 06/2013 and 02/2017, 495 pts were included in 42 centers. Data available for 463 pts. Median age 79 years (70-95) with 46% over 80. 74% males. 67% of SGE was performed by oncologists and 33% by nurses/clinical research staff. Mean time to complete SGE was 22 minutes. After SGE, 72% pts were classified as unfit. 52% of pts were further assessed by CGA, 48% among SGE fit pts and 53% among SGE unfit pts. Concordance rate of classification Unfit/Fit by SGE and CGA was 81%. Among pts planned to be treated by curative radiotherapy (RT) or chemo(CT)-RT after oncologic evaluation alone, the planned treatment changed after SGE for 8% of pts: addition of CT/biotherapy to RT for 4% or deletion of CT for 4%. Rate of pts requiring multidisciplinary interventions was significantly higher when the assessment was also performed by geriatricians (71% vs 51%), even after adjusting for frailty.

Conclusions: A CGA-based SGE for use by oncologist in older pts with HNSCC seems feasible and is a first necessary step to define optimal care. Oncologists and geriatricians must keep going developing such close collaboration and data sharing before proposing tailored treatment.

Legal entity responsible for the study: Gustave Roussy

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1051PD A phase 1, multicenter, open-label, dose-escalation, combination study of RM-1929 and photoimmunotherapy in patients with recurrent head and neck cancer

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Background: Patients with recurrent head and neck squamous cell cancer (rHNSCC) have a poor prognosis once they have failed definitive treatment. We have completed a Phase 1 dose-escalation study of a unique targeted light activated drug conjugate RM1929 consisting of the EGFR-directed monoclonal antibody cetuximab conjugated to the phthalocyanine dye IRDye 700DX.

Methods: This was a Phase I study of rHNSCC patients who could not be satisfactorily treated with surgery, radiation, or platinum chemotherapy. The study included a drug dose-escalation with a fixed fluence light application to determine the drug dose that could be safely given to activate the pharmacodynamics of anticancer responses. Twenty-four hours after drug infusion non-thermal red light was applied to the tumors either on the surface for mucosal/skin disease or within the tumor via fiber optic diffusers for submucosal or nodal disease. Primary safety endpoints were assessed at 1 week and secondary efficacy endpoints were assessed at 1 month post treatment.

Results: Nine patients were enrolled in the 3 cohort dose escalation study. There were no dose-limiting toxicities and the drug dose and light fluence for treatment was determined. No photosensitivity reactions were observed at any drug dose during solar simulator testing. Four patients experienced 3 SAEs that were probably or possibly related to treatment including oral pain, tumor hemorrhage, and tumor pain. For 8 patients who were assessed for best overall response rate after a single cycle of treatment using clinical and RECIST 1.1, the objective response rate (ORR) was 75% (6/8) with 3 complete responses which were durable (4-16 months). The disease control rate was 100% (DCR). 7/8 patients showed a decrease in tumor density, consistent with post-treatment necrosis.

Conclusions: The phase 1 dose escalation study demonstrated the safety and tolerability of photoimmunotherapy with RM1929. We have observed improvement in clinically significant endpoints in patients with rHNSCC who do not have other treatment options.

Clinical trial identification: NCT02422979

Legal entity responsible for the study: FDA

Funding: Aspyrian Therapeutics

Disclosure: All authors have declared no conflicts of interest.

1052PD First-line paclitaxel plus carboplatin with/without bevacizumab in recurrent or metastatic nasopharyngeal carcinoma: A multicenter, randomized, open-label, phase II trial

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Background: This trial was conducted to investigate the efficacy and safety of paclitaxel plus carboplatin with/without bevacizumab in recurrent or metastatic nasopharyngeal carcinoma (NPC).

Methods: Patients with recurrent or metastatic NPC recruited from 12 hospitals in China were randomly assigned to receive carboplatin (area under the curve 6) and paclitaxel (175 mg/m^2) intravenously on day 1 once per 3 weeks for a maximum of 6 cycles, with (CP+B) or without (CP) bevacizumab (7.5 mg/kg) intravenously on day 1 of each cycle, until disease progression, untolerable toxicity, or death. The primary endpoint was progression-free survival (PFS). Secondary end points were objective response rate (ORR), disease control rate (DCR), overall survival (OS) and safety. This study is ongoing and registered with ClinicalTrials.gov (NCT02250599).

Table: 1052PD

Efficacy	CP+B (n = 41)	CP (n = 39)	p	
ORR [n (%)]	35(85.4)	27(69.2)	0.084	
DCR [n (%)]	40(97.6)	39(100%)	1.000	
PFS [m (95%CI)]	7.23 (6.80, 8.71)	7.00 (6.37, 8.41)	0.506	
Common drug-related AEs	**CP+B (n = 42)**		**CP (n = 40)**	
	All grades (%)	**Grade 3-4(%)**	**All grades (%)**	**Grade 3-4(%)**
Leucopenia	39(92.9)	14(33.4)	40(100)	16(40)
Neutropenia	33(78.7)	16(38.2)	40(100)	21(52.5)
Aneamia	29(69.1)	7(16.7)	27(67.5)	2(5.0)
Thrombocytopenia	23(54.8)	1(2.4)	20(50)	1(2.5)
ALT increased	10(23.9)	2(4.8)	12(30)	0
AST increased	5(12)	0	9(22.5)	0
Fatigue	9(21.4)	0	10(25)	0
Peripheral neuropathy	10(23.9)	0	19(47.5)	0
Nasal bleeding	4(9.5)	0	2(5)	0
Hemoptysis	1(2.4)	0	2(5)	0

Results: Between Jun 8, 2015 and Jan 1, 2017, 80 patients were randomly assigned, 41 to the CP+B group and 39 to the CP group. ORR showed a numerical improvement with CP+B group (85.4% vs 69.2%) although with no statistical difference ($p = 0.084$). The median PFS was 7.23 months in the CP+B group and 7.00 months in the CP group ($p = 0.506$). OS had not yet matured. Safety was similar in two groups. No bevacizumab related serious adverse events were observed specially including bleeding.

Conclusions: CP+B regimen showed a numerical advantage in ORR among NPC patients. Given the limited sample size of our study, further research is needed to evaluate efficacy of bevacizumab in NPC.

Clinical trial identification: NCT02250599 Protocol Registration Receipt: 09/26/2014

Legal entity responsible for the study: the Institutional Review Board and academic committee of Sun Yat-Sen University Cancer Center

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1053PD Refining staging system for nasopharyngeal carcinoma treated with intensity-modulated radiation therapy

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Background: We incorporated baseline plasma EBV DNA into refinement of stage groups for nasopharyngeal carcinoma (NPC) treated with radical intensity-modulated radiation therapy (IMRT).

Methods: Patients with non-metastatic NPC treated with radical IMRT +/- adjunct chemotherapy based on 7th edition of American Joint Committee on Cancer (AJCC) system were recruited prospectively from 2010 to 2016. All patients had baseline and serial post-IMRT plasma EBV DNA (in copies/ml) measured and were staged with MRI and PET-CT. Recursive partitioning analysis (RPA) with repeated internal validations derived new stage groups with incorporation of baseline plasma EBV DNA. Multivariable analyses were used to calculate adjusted hazard ratios (AHRs) to derive a new set of AHR stages. Comparison of performance of survival prediction among these 3 sets of stage groups was done to find the best-performing stage set.

Results: The cohort included 520 patients treated with IMRT +/- adjunct chemotherapy with a median follow-up of 5.0 years. They were re-staged based on 8th edition of AJCC system. 5-year overall survival (OS) and cancer-specific survival (CSS) were as follows: stage I (OS 89.5%; CSS 100%), II (OS 87.8%; CSS 94.7%), III (OS 85.0%; CSS 90.0%) and IVA (OS 74.4%; CSS 79.9%) ($p = 0.058$ and $p = 0.003$ respectively). RPA derived NPC into 3 new stages with corresponding OS and CSS: RPA-I (T1-T4N0-N2 & T1-T2N3 & EBV DNA $<=2000$) (OS 89.1%; CSS 95.2%), RPA-II (T1-T4N0-N2 & T1-T2N3 & EBV DNA >2000) (OS 80.5%; CSS 84.1%) and RPA-III (T3-T4N3) (OS 58.2%; CSS 67.1%) (both $p < 0.001$ and $p < 0.001$ respectively). AHR (I: T1-T2N0-N2; II: T3-T4N0-N2 & T1-T2N3; III: T3-T4N3) after adjusting age, smoking status, treatment (chemoradiation vs. IMRT alone), baseline LDH and plasma EBV DNA also yielded a valid classification ($p < 0.001$ for both OS and CSS) but was worse on survival prediction compared to RPA. The RPA stages demonstrated better survival prediction especially on CSS after 1000 bootstrapping replicates (bootstrap scores – OS: 0.469; CSS: 0.752) than AHR stages (OS: 0.436; CSS: 0.206) and 8th edition AJCC (OS: 0.095; CSS: 0.043).

Conclusions: A novel RPA-based TNM stage groups revealed significantly better survival prediction compared with the 8th edition AJCC and AHR stages.

Clinical trial identification: NCT02476669

Legal entity responsible for the study: Department of Clinical Oncology, The University of Hong Kong and Clinical Oncology Center, The University of Hong Kong-Shenzhen Hospital

Funding: SK Yee Medical Foundation

Disclosure: All authors have declared no conflicts of interest.

1054PD A New Classification for Nasopharyngeal Carcinoma

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Background: This study is to develop and validate a new classification for nasopharyngeal carcinoma (NPC).

Methods: Fifteen hundred and twenty-eight (1528) newly diagnosed NPC patients treated between 1995 and 2010 were included in this study. Seven hundred and one patients ($n = 701$) were treated with 3D conformal radiotherapy (3D-RT) and 827 patients were treated with IMRT. Cox proportional hazards model was used to select the significant split node to partition patients into the different risk group. Recursive partitioning analysis derived a new classification in patients treated with 3D-RT objectively. This new staging system was then validated in patients treated with IMRT.

Results: The median follow-up interval was 84.6 months (ranging 2-175 months). According to the 7th AJCC staging system, the stage I patients showed a 5-year overall survival (OS) rate of 93.0%, stage II of 94.5%, stage III of 87.5%, stage IVA of 71.5%, stage IVB of 61.3%, and stage IVC of 5.8% ($p < 0.0001$). In the validation group ($n = 827$), the Group I in new system was patients with stages of T1-3N0-1 and T1N2 ($n = 364$); their 5-year OS was 92.4%. The Group II was patients with stages of T2N2 and T3N2 ($n = 175$); thier 5-year OS was 86.0%. The Group III was patients with stages of any T4 and N3 ($n = 249$); their 5-year OS was 72.0%. The Group IV was patients with distant metastasis ($n = 36$); their 5-year OS was 17.9%. This new classification system will be compared to the 8th AJCC staging system.

Conclusions: We propose a new staging system for NPC, which distributes more patients in the early stage.

Table: 1054PD Patient Distribution According to Chinese 2008 and the 7th AJCC staging systems

Stage	Chinese 2008 staging	2010 AJCC staging	Current proposal
Stage I	2.3%	2.3%	42.9%
Stage II	11.0%	23.7%	21.9%
Stage III	39.4%	49.1%	30.0%
Stage IV	47.3%	24.9%	5.2%

Legal entity responsible for the study: None

Funding: Koo Foundation Sun Yat-Sen Cancer Center

Disclosure: All authors have declared no conflicts of interest.

1055P Nivolumab vs investigator's choice (IC) in patients with recurrent or metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN): treatment effect on clinical outcomes by best overall response in checkmate 141

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Background: In CheckMate 141, nivolumab monotherapy significantly prolonged overall survival (OS) vs IC (median [95% CI]: 7.5 [5.5, 9.1] mo vs 5.1 [4.0, 6.0] mo) and doubled response rate (13.3% vs 5.8%) in patients (pts) with R/M SCCHN. Here, we describe clinical outcomes by best overall response for the nivolumab and IC arms.

Methods: CheckMate 141 (NCT02105636) was a randomized, open-label, phase 3 trial in which pts ($N = 361$) with R/M SCCHN who progressed on or within 6 mo of platinum-based therapy were randomized 2:1 to nivolumab 3 mg/kg every 2 weeks ($n = 240$) or IC of methotrexate, docetaxel, or cetuximab ($n = 121$). We analyzed the

Table: 1055P

	CR/PR		SD		PD	
	Nivolumab (n = 32)	**IC (n = 7)**	**Nivolumab (n = 55)**	**IC (n = 43)**	**Nivolumab (n = 100)**	**IC (n = 42)**
Median OS, mo(95% CI)	NR (NR, NR)	13.6 (8.9, NR)	10.4 (8.7, 15.2)	7.1 (5.4, 9.5)	5.7 (4.8, 7.8)	4.5 (3.6, 5.8)
HR (95% CI)	0.08 (0.01, 0.47)		0.53 (0.33, 0.85)		0.74 (0.51, 1.09)	
12-mo OS rate, % (95% CI)	96.8 (79.2, 99.5)	57.1 (17.2, 83.7)	46.1 (32.4, 58.7)	29.4 (16.4, 43.7)	21.4 (13.9, 30.1)	11.9 (4.4, 23.6)
18-mo OS rate, % (95% CI)	86.1 (67.0, 94.6)	38.1 (6.1, 71.6)	32.6 (20.0, 45.8)	11.7 (3.6, 25.0)	3.0 (0.6, 8.9)	4.8 (0.5, 17.2)

NR = not reached

primary endpoint of OS and additional endpoint of safety by best overall response (complete or partial response [CR/PR], stable disease [SD], or progressive disease [PD]), assessed by investigators per RECIST 1.1 every 6 weeks beginning at week 9.

Results: The minimum follow-up was 11.4 mo. Baseline demographics were similar across response groups and treatment arms. Median duration of therapy for nivolumab-treated pts with CR/PR, SD, and PD was 12.5 mo, 4.2 mo, and 1.6 mo, respectively. Estimates of median OS, 12-mo, and 18-mo survival rates favored nivolumab vs IC in the CR/PR and SD response groups (Table). The incidence of grade 3–4 treatment-related adverse events was lower for nivolumab vs IC within each of the response groups (CR/PR, SD, and PD).

Conclusions: Pts with CR/PR and SD had improved median OS and survival rates with nivolumab relative to single-agent standard therapy. Nivolumab's safety profile was favorable vs IC, including for pts with CR/PR whose median duration of therapy was greater than a year.

Clinical trial identification: NCT02105636

Legal entity responsible for the study: Bristol-Myers Squibb

Funding: Bristol-Myers Squibb

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1056P Estimated costs of treatment-related adverse events (TRAEs) for recurrent or metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN) in the checkmate 141 trial

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Background: Nivolumab, a programmed death-1 (PD-1) immune checkpoint inhibitor antibody, is approved in the United States and the European Union for treatment of SCCHN progressing on or after platinum-based chemotherapy. In the phase 3 CheckMate 141 trial, nivolumab significantly improved overall survival vs investigator's choice (IC) of standard, single-agent systemic therapy (methotrexate, docetaxel, or cetuximab) in patients with R/M SCCHN. This study assessed the estimated costs of managing grade 3–4 TRAEs requiring treatment in CheckMate 141.

Methods: The frequency, grade, and attribution of TRAEs for which treatment was received were extracted from CheckMate 141 patient-level safety data. Grade 3–4 TRAE treatment costs were estimated based on principle diagnosis codes of the International Classification of Disease, 9th Revision in the Healthcare Cost and Utilization Project National Inpatient Sample data (2012–2014), adjusted to reflect 2013-equivalent US costs.

Results: Among the 347 patients in the safety population, 236 received nivolumab and 111 received IC. A total of 88 grade 3–4 TRAEs requiring treatment were observed: 28 among patients receiving nivolumab and 60 among patients receiving IC. The cost of managing TRAEs per treated patient was 4.5 times higher in the IC arm ($4913) than in the nivolumab arm ($1072). Patients receiving docetaxel and methotrexate had the highest incidence of TRAEs and estimated TRAE management costs (Table).

Table: 1056P

	Nivolumab (n = 236)	IC (combined) (n = 111)	IC		
			Cetuximab (n = 13)	**Docetaxel (n = 52)**	**Methotrexate (n = 46)**
Number of grade 3–4 TRAEs requiring treatment (%)	28/88 (31.8)	60/88 (68.2)	2/60 (3.3)	36/60 (60.0)	22/60 (36.7)
Total estimated cost of managing grade 3–4 TRAEs, $	253,067	545,374	17,855	333,307	194,211
Cost of managing grade 3–4 TRAEs, mean per treated patient, $	1072	4913	1373	6410	4222

Conclusions: Patients with platinum-refractory R/M SCCHN treated with nivolumab had fewer grade 3−4 TRAEs, lower estimated total costs of managing TRAEs, and reduced TRAE costs per treated patient compared with standard, single-agent systemic therapy.

Clinical trial identification: NCT02105636

Legal entity responsible for the study: Bristol-Myers Squibb

Funding: Bristol-Myers Squibb

Disclosure: S. Bobiak: Former Bristol-Myers Squibb employee (at the time the submitted work was started); Spouse is current employee of Bristol-Myers Squibb. J.W. Shaw, M. Contente, B. Korytowsky: Bristol-Myers Squibb employee and shareholder. D.D. Stenehjem: Consulting fees from Bristol-Myers Squibb; Unrestricted research grant (unrelated to work regarding the content of this abstract) from Bristol-Myers Squibb. All other authors have declared no conflicts of interest.

1057P Phase I trial of cetuximab, intensity modulated radiotherapy (IMRT), and ipilimumab in previously untreated, locally advanced head and neck squamous cell carcinoma (PULA HNSCC)

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Background: Concurrent IMRT with cetuximab (C), an EGFR-specific antibody for PULA HNSCC is suboptimal for intermediate-risk (IR) or high risk (HR) HNSCC. CTLA-4+ Tregs dampen cellular immunity and correlate negatively with clinical outcomes. Thus, we conducted a phase I study adding ipilimumab (ipi), an anti-CTLA-4Ab to standard C-IMRT in patients (pts) with intermediate or high risk PULA HNSCC.

Methods: Key eligibility: stage III-IVb PULA HNSCC [pharynx, larynx]; highrisk [HPV-] or intermediate risk [HPV+ and either: ≥ 10 pack-year tobacco and ≥ N2 disease; or T4 or N3 disease]. A phase I [3 + 3] dose escalation design was used to establish a recommended phase II dose [RP2D). Dose limiting toxicity [DLT] was defined as any grade 4 adverse event [AE] except in-field radiation dermatitis or any immune-related [ir] AE requiring ≥ 2 weeks of systemic steroids.

Results: From July 2013-May 2016, 18 pts enrolled: 5 larynx, 3 hypopharynx, 3 HPV-oropharynx, 7 HPV+ oropharynx; 14 smokers; 2 stage III, 13 stage IVa, 3 stage IVb. Two of 6 pts incohort 1 experienced grade 3 dermatologic DLT's: perforating folliculitis and autoimmune dermatitis. Cohort -1 was expanded to N = 12 without DLT's. irAE included: grade 1, 2, and 3 dermatitis [2, 1, and 3 cases], grade 4 colitis [1], and grade 1 hyperthyroidism [1]. Four pts recurred, 3 of whom died. Five patients remain disease-free for >2 years. Median follow up for disease-free patients was 14 months [range 5 - 37 months]. The probability of 2-year overall survival was 71% [95% CI: 49% - 100%]. The two-year probability of progression- free survival was 77% [95% CI: 59% - 100%]. Immune biomarkers demonstrated modulation of suppressive regulatory T cell [Treg] subsets.

Conclusions: Ipi plus C-IMRT is tolerable and yields acceptable survival without cytotoxic chemotherapy for IR and HR patients. The RP2D for ipi plus C-IMRT is 1mg/kg weeks 5, 8, 11, and 14. Treg biomarkers are modulated by this type of immunotherapy.

Clinical trial identification: Clinical trial information: NCT01935921

Legal entity responsible for the study: University of Pittsburgh Cancer Institute

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Disclosure: R.L. Ferris: Astra-Zeneca/MedImmune: Advisory Bd, Clin trial, Research Funding Bristol-Myers Squibb: Advisory board, Clin trial, Research funding Lilly: Advisory Board Merck: Advisory Board, Clin trial Pfizer- Advisory Board VentiRx Pharmaceuticals: Research funding. D. Petro: Celgene - Advisory Board. J. Bauman: Scientific Consulting: Merck, Merck/EMD Serono, Eli Lilly, Kolltan. All other authors have declared no conflicts of interest.

1058P Does hyper-progression exist among head and neck cancer patients treated with immunotherapy?

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Background: Immunotherapy (IM) improves survival (OS) in recurrent/metastatic squamous cell carcinoma of the head and neck (HNSCC) patients after platinum progression. Hyper-progression (HP) is a pattern of accelerated tumor growth with ECOG deterioration (ECOGdt) that has been described in patients (p) with solid tumors within the first weeks of IM.

Methods: HP is defined by twofold increase in tumor growth rate (TGR) (1). Our aim was to detect HP in a cohort of HNSCC p treated with IM in clinical trials in 2 cancer centers (ICO, VHIO). 1 S Champiat. Clin Cancer Res, 2016.

Results: From 08/2014 to Dec/2016, 69p were included in IM trials. Among them, 46p were evaluable for TGR. Baseline characteristics and IM are listed in Table. After a median follow-up of 9.4 months (m) (1-27), 36p have progressed and 24 have died. Median overall survival (mOS): 14m (8-20), percentile 75% 5m (3-7). TGR decreased in 33 p. TGR increased in 13p, presenting two-fold TGR in 2p, with 2 IM discontinuation within 2 months and 1 ECOGdt, with no differences in mOS compare to the rest (p = 0.8). We also identify 9p with progression within 2m and rapid ECOGdt, which were defined as early progressors (EP). A comparative analysis between EP and no EP was performed (Table). Within EP p, there is a lower proportion of objective response (OR), PDL-1 positivity and cisplatin sensitive (CS) tumors (p > 0.1). EP p had significantly higher proportion of tumor complications (p = 0.013) and worse mOS: 3m (0.8-5.9) vs 15m (3.9-26), HR 3.9 (1.2-10) p 0.008.

Conclusions: In our cohort, we did not detect HP as previously defined. However, there is a proportion of p that has poor survival due natural HNSCC history, these p lack of benefit from IM monotherapy and other strategies should be explored.

Legal entity responsible for the study: Catalan Institute of Oncology

Funding: None

Disclosure: All authors have declared no conflicts of interest.

Table: 1058P

	All cohort n = 46 n (%)	Progression n = 36		
		No EP n = 27	EP n = 9	p value
Age	58	56	58	0.6
Male	39 (85)	22	8	1
Smokers	42 (91)	24	9	0.6
PDL-1 n = 33 Positive Negative	21 (45) 22 (48)	14 11	2 6	0.2
Locoregional disease (LRD) Metastatic without LRD	33 (71) 13 (29)	22 5	5 4	0.2
Previos systemic therapy 0 1 2 ≥3	3 (7) 11 (24) 30 (65) 2 (4)	1 5 20 1	0 2 6 1	0.5 1 0.7 0.4
OR (n = 44)	11 (25)	7	0	0.1
TGR increase	13 (28)	9	2	0.7
CS (n = 40)	23 (58)	17	4	0.4
AntiPD-1 AntiPDL-1 AntiPDL-1 + CTLA-4 Immunomodulator (IMD) AntiPDL-1 + IMD AntiPD-1 + CT	9 (20) 11 (24) 16 (35) 4 (9) 2 (3) 4 (9)	5 8 7 4 1 2	2 1 5 0 1 0	0.6 0.5 0.1 0.5 0.4 1
Tumor complications	8 (17)	3	5	0.013

1059P PD-L1 Detection and Assay Performance in Squamous Cell Carcinoma of the Head and Neck Using PD-L1 IHC 28-8 pharmDx

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Background: Detecting PD-L1 protein expression by immunohistochemistry has shown to be effective in identifying patients who may benefit from treatment with PD-1 targeted immune checkpoint inhibitors. The PD-L1 IHC 28-8 pharmDx assay has been applied in formalin-fixed, paraffin-embedded (FFPE) squamous cell carcinoma of the head and neck (SCCHN) tissues for measuring PD-L1 expression and its associated treatment effect with nivolumab. Assay performance results of PD-L1 IHC 28-8 pharmDx in SCCHN, including validation in external reproducibility, are described.

Methods: Antigen retrieval was conducted on Dako PT Link and automated staining was performed with Autostainer Link 48 platform using the PD-L1 IHC 28-8 pharmDx protocol, per instructions for use. The PD-L1 staining was assessed by tumor proportion score to report the percentage of PD-L1 expression in invasive SCCHN. Assay performance was validated at the $\geq$ 1% expression level on commercially procured FFPE SCCHN specimens.

Results: PD-L1 expression was measured on 236 unique specimens originating from squamous cell carcinoma of the tongue, tonsil, nasopharynx, oropharynx, hypopharynx, and larynx. The assay demonstrated acceptable sensitivity and reported a large range of PD-L1 expression from 0 to 95% positive tumor cells and 0 to 3+ staining intensity. Acceptable correlation was observed between primary and metastatic specimens and between "sister" blocks from the same patient. Validation of assay precision and robustness (to target retrieval solution pH, target retrieval solution temperature, target retrieval time, and cut section thickness) demonstrated agreement estimates above 97.5% with the lower bound of two-sided 95 percent confidence intervals at 95% or higher. When tested in external sites, intra- and inter-site reproducibility, and intra- and inter-observer agreements were estimated above 94% with the lower bound of two-sided 95 percent confidence intervals at 88% or higher. Stability of PD-L1 staining in aged cut sections demonstrated interim stability at 4 months with ongoing evaluation.

Conclusions: PD-L1 IHC 28-8 pharmDx has shown to be reproducible and robust in detecting PD-L1 expression in FFPE human SCCHN specimens using the Autostainer Link 48.

Legal entity responsible for the study: Agilent Technologies, Inc.

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Disclosure: S. Alvarez: Currently employed by a for-profit health care company, Agilent Technologies. Own stock in a for-profit health care company, Agilent Technologies. J. Chan, C. Felten: Employed, leader for, and has ownership in Gemini Diagnostics. Paid consultant for Agilent Technologies. J. William: Employed by a diagnostic laboratory, Neogenomics. Was in a paid consulting role for Agilent Technologies in the last 2 years. D.A. Hanks: Employed and holds leadership for Premier Pathology Laboratories, Inc. Employed by Agilent Technologies, Inc. Holds intellectual property relating to health and medicine in the last 2 years while working with Agilent Technologies. A. Northrup: Employed by Agilent Technologies and owns stock in Agilent technologies. Has been reimbursed for travel, accommodations, or other expenses by Agilent Technologies in the last 2 years. D. Jaiswal, M. Jansson, T. Phillips: Employed by Agilent technologies. And own stock in Agilent Technologies. A. Segal: Was employed by Agilent Technologies and owns stock in Agilent Technologies. I. Satnick, H. Little, B. Wynne, C. Pierce: Employed by Agilent Technologies. H. McDonald: Employed by Agilent Technologies. Was employed by Baster/Baxalta/Shire in the last two years. Owns stock in Shire, Inc. J. Carnahan: Employed by Agilent Technologies. Was employed by Agensys in the past 2 years and received research funding and paid travel expenses from Agensys. Owns stock in Amgen. S.Y. Reddy: Employed by Agilent and owns stock in Agilent Technologies. H.D. Inzunza: Was employed by Bristol-Myers Squibb and is employed by Halozyme. E. Oroudjev: Employed by Agilent Technologies. Is in leadership role for Agilent Technologies. Owns stock in Agilent Technologies.

1060P Programmed death ligand-1overexpression is a poor prognostic factor for Human papillomavirus-positive tonsillar squamous cell carcinoma

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Background: Programmed death-ligand 1 (PD-L1) plays a key role for immune evasion, contributing to carcinogenesis and tumor progression. Tonsillar squamous cell carcinomas (TSCCs) are the most common human papillomavirus (HPV)-associated oropharyngeal cancers and they frequently present with locally advanced diseases and cervical metastases, which are associated with poor prognoses. Recent studies have reported the close association between PD-L1 and HPV in head and neck SCCs. However, its clinical and prognostic significances in TSCCs remain controversial.

Methods: Immunohistochemical analysis of PD-L1 was performed in 79 formalin-fixed paraffin-embedded blocks of surgically resected specimens. Peptide nucleic acid-based HPV chip test was used for detection of HPV.

Results: PD-L1 expression was observed in 19 cases (24.1%), and clinicopathological features such as invasion to base of tongue, lymphatic invasion, infiltrative tumor border, younger age (<60 years), left side location, and lymph node metastasis represent significant risk factors associated with PD-L1 overexpression in TSCCs. HPV tended to be associated with PD-L1 overexpression, which showed borderline statistical significance ($P = 0.066$). PD-L1 expression was a strong indicator for poor overall survival but not for disease-free survival. Notably, PD-L1 overexpression had significant effects on worse overall and disease-free survivals in HPV-positive TSCCs. Multivariate analysis revealed that PD-L1 overexpression was an independent prognostic factor for overall survival ($P = 0.049$, hazard ratio 2.750).

Conclusions: PD-L1 overexpression may predict a poor prognosis and a high risk of recurrence in TSCC patients, especially in HPV-positive tonsil cancers, implying PD-L1 could be potent candidates for a new prognostic and predictive biomarker in tonsil cancers.

Legal entity responsible for the study: none

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1061P The prognostic role of PD-L1 expression in tumor and immune cells in oral cavity squamous cell carcinoma

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Background: The programmed death-ligand 1 (PD-L1) has an important role in anticancer immunity. The aim of our study was to examine the expression and prognostic value of PD-L1 in tumor and immune cells in patient with squamous cell carcinoma of oral cavity (OCSCC).

Methods: We detected tumor samples of 60 patients with OCSCC with stage I - IVB (37 men, 23 women; median age 59). We examined demographic data, clinical stage, tumor morphological characteristics and expression of PD-L1 in tumor and immune cells (clone BCDdx1020) by immunohistochemistry (55 samples were acceptable).

Results: The expression level in tumor cells varied from 0% to 70%: in 24 (43,64%) samples expression of PD-L1% were negative (0%), in 9 (16,36%) - from 1 to 4% (low rate), in 17 (30,91%) - from 5 to 49% (moderate rate) and in 5 (9,1%) - more than 50% (high). In immune cells expression of PD-L1 varied from 0% to 15%: in 7 (12,73%) samples - negative (0%), in 30 (54,55%) - from 1 to 4% (low), in 13 (23,64%) - from 5 to 9% (moderate) and in 5(9,10%) - >10% (high). In 5 samples with high level PD-L1 expression in tumor expression PD-L1 in immune cells was negative. Median OS of patients with PD-L1-negative' tumor was 17 mo (95% CI 8-185), with low rate (1-4%) of PD-L1 expression - 9 mo (95% CI 2-36), with moderate rate (5-49%) - 13 mo (95% CI 7,5-19) and median OS in patients with high rate (>50%) not reached for this time and mean of OS is 55 mo ($\sigma = 14{,}722$) (95% CI 26-84). Median OS of patients with negative PD-L1-status in immune cells was 12 mo (95% CI 4-185), with low rate (1-4%) PD-L1 in immune cells - 13 mo (95% CI 7,5-34,5), with moderate rate (5-9%) - 15 mo (95%CI 9-15) and with hight rate (>10%) - 17 mo (95%CI 3-36) with strong trend of increasing OS with rise of PD-L1 expression in immune cells.

Conclusions: PD-L1 expression in tumor and immune cells are favourable prognostic factors for oral cavity squamous cell carcinoma.

Legal entity responsible for the study: Svetlana Kutukova

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1062P Immune profile analysis of head and neck squamous cell carcinoma before and after neoadjuvant treatment with the IRX-2 regimen

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Background: IRX-2 is an injectable cancer immunotherapy composed of cytokines purified from stimulated peripheral blood mononuclear cells. In a phase 2a trial

(n = 27), neoadjuvant IRX-2 significantly increased lymphocyte infiltration (LI) into resected head and neck tumors. Increased LI was associated with changes in fibrosis and necrosis in resected tumors, 65% event-free survival (EFS) at 2 years, and 65% overall survival (OS) at 5 years, better than rates for historical matched controls. Patients with LI greater than the median had improved OS compared to those below the median. This substudy was undertaken to define the mechanisms responsible for the increase in LI with neoadjuvant IRX-2.

Methods: Matched pre- and post-treatment tumor specimens from 7 phase 2a study patients were interrogated with two immune-profiling technologies, multiplex immunohistochemistry (IHC, PerkinElmer, Waltham, MA) and transcriptome analysis (NanoString Technologies, Seattle, WA).

Results: Multiplex IHC provided detailed visualization and quantitation of various immune cells in the tumor microenvironment (TME), supporting previous phase 2a pathology findings. Transcriptome analysis provided a global snapshot of the TME, quantitative information on immune cell subsets, and insights into possible mechanisms for changes in LI. Consistent with IRX-2 activation of multiple immune cells in the TME, mRNA expression of B cell, CD4+ T cell, CD8+ T cell, and dendritic cell functional genes was increased on average by 87%, 106%, 6%, and 130%, respectively, following treatment with IRX-2. Increases in chemokine gene expression were observed, suggesting that IRX-2-induced production of chemokines may in part drive tumor LI. Strong evidence of functional immune activation uncovered by transcriptome analysis included an increase in interferon g pathway gene expression and induction of regulatory checkpoint pathways.

Conclusions: Neoadjuvant IRX-2 promotes tumor LI and prolongs EFS and OS in patients with head and neck squamous cell carcinoma. Immune profile analyses provided insights into the pathways potentially responsible for IRX-2-induced increases in LI and overall immune activation.

Legal entity responsible for the study: IRX Therapeutics, Inc.

Funding: IRX Therapeutics, Inc

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1063P Phenotyping of the immune infiltrate in oropharyngeal squamous cell carcinoma: Focus on materials and methods

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Background: Stromal $CD8^+$ lymphocytic infiltration constitutes an independent prognostic marker for better overall survival in patients with oropharyngeal squamous cell carcinoma (OSCC). However, scoring of (novel) biomarkers is often complicated by the lack of standardised methodology which hampers their use in daily clinical practice. We therefore performed a comparative analysis to evaluate the importance of choice of materials and methods in CD8 assessment in patients with OSCC. Other immune cell markers, that is, CD3 and FoxP3 were taken into account as well.

Methods: Immunohistochemical analysis of CD3, CD8 and FoxP3 was performed on whole-tissue sections from 101 treatment-naive patients with OSCC. A comparison of different immune cell markers was made for biopsy material versus resection material when available. Also, different scoring strategies, that is, quantitative versus semi-quantitative analysis were compared with each other.

Results: Comparison of biopsy material versus resection material proved a good agreement for expression of the $CD3^+$ T cells ($\kappa = 0.712$, $\rho = 0.853$), $CD8^+$ T cells ($\kappa = 0.659$, $\rho = 0.764$) and $FoxP3^+$ T cells ($\kappa = 0.783$, $\rho = 0.802$). The comparison of quantitative versus semi-quantitative assessment demonstrated strong correlations for the $CD3^+$ T cells ($\rho_{biopt} = 0.617$, $\rho_{resection} = 0.634$), $CD8^+$ T cells ($\rho_{biopt} = 0.656$, $\rho_{resection} = 0.675$) and $FoxP3^+$ T cells ($\rho_{biopt} = 0.537$, $\rho_{resection} = 0.720$).

Conclusions: Immunohistochemical analysis of CD3, CD8 and FoxP3 can be performed adequately on biopsy as this appears to be representative for the whole tumour. In addition, this can be done adequately in a semi-quantitative manner without the use of more expensive and time consuming machinery.

Legal entity responsible for the study: Prof. Sylvie Rottey

Funding: agency for Innovation by Science and Technology (IWT)

Disclosure: All authors have declared no conflicts of interest.

1064P High-dose versus low-dose cisplatin with definitive concurrent radiotherapy for squamous cell carcinoma of the head and neck (SCC): An analysis of veteran's health registry data

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Background: Radiotherapy (RT) with concurrent high-dose cisplatin (HDC) improves outcomes for patients (pts) with SCC. Weekly low-dose cisplatin (LDC) is a widely used alternative approach. The comparative effectiveness and safety of these approaches is unknown. We compared the outcomes of pts treated with HDC and LDC within the Veteran's Administration Corporate Data Warehouse (CDW).

Methods: We identified stage III-IVb SCC patients treated non-surgically with RT and HDC or LDC from 2002 to 2014 in the CDW. Pts were grouped by the dose of their first cycle (HDC vs LDC; intent-to-treat). Variables including cancer site, stage, smoking/alcohol use, and comorbidities were used to generate propensity scores (PS) for the use of HDC. We compared overall survival (OS) by treatment group using Cox regression models, adjusting for PS. We also determined the risk of toxicities using PS-adjusted logistic regression models.

Results: A total of 2,820 pts were included in the analysis: 69.7% received HDC (mean initial dose 96 mg/m^2). The mean initial dose of LDC was 30 mg/m^2. HDC pts were younger ($p < 0.001$), with lower creatinine ($p = 0.002$), and lower incidence of baseline neuropathy ($p = 0.02$). In an unadjusted analysis, HDC was associated with improved OS (Table). After PS adjustment, this difference was no longer statistically significant ($p = 0.06$). On primary site sub-analysis, HDC provided a benefit only for oropharyngeal primaries (OP). Adjusting for PS, HDC was associated with more renal failure (OR 2.2, 95% CI 1.6-3), neutropenia (OR 2, 95% CI 1.1-3.5), dehydration/electrolyte disturbance (OR 1.3, 95% CI 1.04-1.6), and hearing loss (OR 1.6, 95% CI 1.3-2).

Conclusions: While HDC does not improve OS over LDC for the overall cohort of patients with SCC receiving RT with definitive intent, it is associated with a survival benefit for patients with OP. HDC is associated with more adverse events.

Legal entity responsible for the study: Keith Sigel

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Table: 1064P OS of HDC vs LDC

Group	Unadjusted HR for OS	95% CI	PS Adjusted HR for OS	95% CI
All patients (n = 2,820)	0.85	0.77-0.94	0.89	0.80-1.01
Oral Cavity (n = 182)	0.77	0.56-1.1	0.72	0.50-1.10
Hypopharynx/Larynx (n = 1,026)	1.00	0.86-1.20	1.1	0.90-1.30
Oropharynx (n = 1590)	0.78	0.70-0.90	0.81	0.69-0.96

Clariant; Caris; ARIAD; Boehringer Ingelheim; Synta; Clovis; Amgen; Synta; Peregrine; Incyte. R.B. Cohen: Takeda scientific ad board Zymeworks, Bristol-Myers Squibb. All other authors have declared no conflicts of interest.

1065P 3-weekly or weekly cisplatin concurrently with radiotherapy for patients with locally advanced squamous cell carcinoma of the head and neck: A multicentre, retrospective analysis

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Background: Concurrent chemoradiotherapy with cisplatin is standard for patients (pts) with loco-regionally advanced squamous cell carcinoma of the head and neck (LA-SCCHN). The standard regimen includes 3-weekly cisplatin, but weekly regimens are often used to lower toxicity. Reaching a cumulative dose of > 200 mg/m^2 cisplatin was shown being associated with improved outcome. We herein investigated cumulative dose reached and toxicity between the both widely used 3-weekly and weekly cisplatin regimens with concurrent radiotherapy.

Methods: Multicentre, retrospective analysis of all patients with LA-SCCHN treated at 3 centers in Switzerland between 06/2008 and 12/2015. We used descriptive statistics and logistic regression (uni- and multivariable) to investigate the association between the chosen cisplatin regimen (weekly versus 3-weekly) and the chance to reach the cumulative cisplatin dose of > 200 mg/m^2. Landmark approach (8 weeks after start of treatment) was applied for investigating the prognostic impact of the cumulative cisplatin dose on survival using Cox regression techniques.

Results: We included 314 eligible pts (3-weekly schedule, N = 127; weekly schedule, N = 187). Median cumulative cisplatin dose was 200 mg/m^2 (IQR 150-300) for pts treated with a 3-weekly schedule and 160 mg/m^2 (120-240) for the weekly schedule, consequently more pts treated with a 3-weekly schedule reached a cumulative dose >200 mg/m^2 (75.6% vs. 47.1%, $p < 0.001$). This association was also observed in multivariable analysis adjusted for age and sex (OR 3.46, 95% confidence interval [CI], 2.1 - 5.7). The 3-weekly regimen led to a higher rate of renal toxicity (33.1% vs. 20.9%, $p = 0.022$), but not ototoxicity (15% vs. 12.8%). In the landmark analysis, we could not confirm that a cisplatin dose >200 mg/m^2 is associated with better survival (HR 1.3, 95% CI 0.8 -1.9).

Conclusions: Significantly more patients receive a cumulative of dose of > 200 mg/m^2, when treated with a 3-weekly schedule compared to weekly dosing. This comes at the cost of more renal toxicity. Due to the non-randomized nature of this analysis, no conclusions on the efficacy of the respective schedules should be drawn.

Legal entity responsible for the study: University Hospital Basel

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1066P Hyperfractionated twice daily re-irradiation (bid re-RT) and chemotherapy (CT) for locoregionally recurrent head and neck squamous cell carcinoma (LR HNSCC): A systematic review (SR)

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Background: Re-RT +/- CT is a salvage option for patients (pts) with LR HNSCC in a previously radiated field, although efficacy and toxicity, and the optimal treatment regimen remains undefined due to a lack of randomized trials. Hyperfractionated bid re-RT, by reducing the dose per fraction may improve radiation (RT) therapeutic ratio and is increasingly used in LR HNSCC. The aim of this SR is to assess the treatment outcomes of bid re-RT + CT in LR HNSCC.

Methods: We conducted a SR of MEDLINE, EMBASE and the Cochrane library up to Nov 2016 for clinical trials of bid re-RT + CT in pts with LR HNSCC. Paired reviewers selected studies for inclusion and extracted data. Individual patient level overall survival (OS) data were extracted where possible from published Kaplan-Meier (KM) curves to construct an aggregate KM curve.

Results: We identified 10 clinical trials (all were phase 1 or 2) with 404 pts. Median (of reported medians) prior RT dose was 64Gy, and median time from prior RT was 30.9m. Seventy-three and 156 pts respectively had CT and surgery as part of 1st line treatment. Median re-RT dose was 60Gy administered as continuous or split courses. The re-RT fields consisted of gross tumor volume plus a minimum margin (range 1-2cm). All CT regimens were combinations either with cisplatin (n = 6) or 5-FU (n = 4), given concurrently with (n = 9) or prior to (n = 1) re-RT. Twenty-eight (7%) pts had debulking surgery prior to re-RT. In pts who were analyzable for toxicities, acute events (>/=grade 3) were reported in 252 of 377 (67%) pts and late events (>90d post re-RT) in 87 of 333 (26%) pts. Treatment-related deaths occurred in 26 (6%) pts, mostly due to infection or vascular events. Of the 5 trials with extractable KM curves, estimated median OS was 10.2m (95% CI 8.7-12.6m); 1- and 3-y OS rates were 46.8% and 11.2% respectively. No differences were observed in median OS and toxicity rates based on CT type (Wilcoxon test).

Conclusions: This is the 1st aggregate analysis of bid re-RT and CT in LR HNSCC. Long-term OS was observed in a subset of pts, however treatment-related morbidity was apparent. The optimal re-RT and CT regimen is still undefined and further study is required.

Legal entity responsible for the study: None

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1067P Raltitrexed versus 5-fluorouracil with cisplatin and concurrent radiotherapy (CCRT) for locally advanced head and neck squamous cell carcinoma (LA-HNSCC): A randomized controlled multi-centered trial

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Background: CCRT has been considered to be the standard of treatment for LA-HNSCC. However, patients receiving CCRT experience a substantial number of treatment-related adverse events, primarily causing oropharyngeal mucositis(OM) and leading to interruption or discontinuation of treatment. Raltitrexed is a specific thymidylate synthase inhibitor with a convenient administration, acceptable toxicity and radiosensitizing property, as the published phase I/II trials have shown. This study aimed to compare the clinical efficacy and toxicity of cisplatin with raltitrexed (RP) or 5-fluorouracil (FP) for LA-HNSCC.

Methods: Eligible patients with LA-HNSCC were randomly assigned in a 1:1 ratio to receive CCRT with either RP or FP. The RP group consisted of 2.5mg/m^2 intravenous raltitrexed on day 1 and 25 mg/m^2 intravenous cisplatin on days 1-3. The FP group consisted of continuous intravenous infusions of 600 mg/m^2 5-fluorouracil on days 1-5 and 25 mg/m^2 intravenous cisplatin on days 1-3. Chemotherapy was administrated concurrently with radiotherapy and was repeated every 3 weeks with completion of at least 2 cycles. Primary endpoint was PFS. Secondary endpoints were complete response rates(CRR), OS and safety.

Results: A total of 108 patients with LA-HNSCC enrolled in this study, with 52 patients assigned to the RP group and 56 patients to the FP group. There was no significant difference in CRR between the two arms (42.9% vs 26.8%, respectively, $p = 0.074$), with the RP group showing a trend of increased CRR. Data of locoregional control, patterns of failure, and survival required further follow-up. The most frequent acute toxicities were bone marrow suppression, gastrointestinal side effects and OM in both arms. The incidence rate of severe OM was significantly lower ($P<0.05$) in the RP group than in the FP group. The incidence of other adverse effects seen in the two arms were similar ($P>0.05$).

Conclusions: The efficacy of the RP regimen was similar to that of the FP regimen. The RP regimen had a tolerable safety profile, with a lower incidence of severe OM and, consequently, an improved quality of life. In conclusion, RP is an effective, well-tolerated regimen for LA-HNSCC.

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Legal entity responsible for the study: Xia He

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1068P The observational ENCORE study: Cetuximab + platinum-based therapy (PBT) for first-line (1L) treatment of patients with recurrent/metastatic squamous cell carcinoma of the head and neck (R/M SCCHN)

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Background: The randomized, phase 3 EXTREME study established cetuximab + platinum + 5-flurouracil (5-FU) followed by cetuximab maintenance until progressive

disease (PD) as the first regimen to yield survival benefits in the 1L management of patients with R/M SCCHN. In EXTREME, the addition of cetuximab increased the overall response rate from 20% to 36%, and extended progression-free survival from 3.3 to 5.6 months and overall survival from 7.4 to 10.1 months. ENCORE is a multinational, non-interventional, prospective, open-label study, seeking to determine how treatment decisions are made, planned and executed by oncologists treating patients with 1L therapy for R/M SCCHN in the real world.

Methods: ENCORE prospectively enrolled 219 patients with R/M SCCHN from Algeria, France, Italy, Portugal and Russia. The recommended treatment for these patients is cetuximab + PBT for up to 6 cycles followed by cetuximab maintenance until PD. Patient characteristics, drugs and schedule were recorded; as the study is still ongoing, safety and efficacy will not be reported here.

Results: ENCORE patients and the EXTREME patients who received cetuximab + platinum + 5-FU had similar performance status (PS: 13.7 and 12% with PS $\geq$ 2, respectively), but dissimilar median age (64 and 56 years, respectively). In ENCORE, 94.1% of patients had a planned treatment of cetuximab + PBT with cetuximab maintenance until PD. The remaining 13 (5.9%) had a fixed treatment duration of 4 to 24 weeks. 37.9% of treatment plans used cisplatin, 61.6% included carboplatin and 3.2% used a taxane. Also, only 53.4% of plans included 5-FU. When developing the treatment plan, 72.1% of all patients were discussed within the context of a multidisciplinary team (MDT). Most plans had the goal of palliative care, and 80% were formulated without a p16 or human papillomavirus status test. Updated data will be presented at congress.

Conclusions: The ENCORE study shows that a real-world R/M SCCHN patient population treated with the EXTREME regimen has diverse characteristics and is treated per current recommendations (e.g. in an MDT setting, with cetuximab until PD).

Clinical trial identification: EMR 62202-566

Legal entity responsible for the study: Merck KGaA, Darmstadt, Germany

Funding: Merck KGaA, Darmstadt, Germany

Disclosure: C. Le Tourneau: Consultancy: Novartis, MSD, Bristol-Myers Squibb, AstraZeneca; Honoraria: Merck Serono J. Schulten: Full Time Employee: Merck KGaA. D. Messinger: Employee/Consultancy: Employee of Prometris GmbH, which has a contract with Merck KGaA regarding statistical consultancy. All other authors have declared no conflicts of interest.

1069P Primary surgery versus chemoradiotherapy for advanced oropharyngeal and hypopharyngeal cancer: A propensity-score matched study using a nationwide database

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Background: Traditionally, advanced head and neck cancer has been managed through surgery with or without postoperative radiotherapy. Studies since the 1980s have been advocating organ preservation therapies by using various combinations of chemotherapy and radiotherapy. For treatment of advanced oropharyngeal and hypopharyngeal cancer, there has been a controversy in choosing between primary surgery and chemoradiotherapy. We aimed at conducting a propensity-score matched study from a national database to investigate the survival after primary surgery with or without postoperative radiotherapy versus chemoradiotherapy in patients with advanced oropharyngeal and hypopharyngeal cancer.

Methods: We identified patients with stage III & IVa oropharyngeal and hypopharyngeal cancers between 2004 and 2009 from Taiwan National Health Insurance Claims Database. The study cohort was followed until 2012. We matched patients who received primary surgery to those who received chemoradiotherapy by propensity score calculated by logistic regression. Age at diagnosis, Charlson comorbidity index score, year of cancer diagnosis, clinical stage, receiving chemoradiotherapy, and receiving radiation therapy were well matched in these two groups. Overall survival and disease-free survival were compared using the Kaplan−Meier method.

Results: We identified 1,603 oropharyngeal and 1,512 hypopharyngeal cancer patients. After propensity score matching, 614 patients with oropharyngeal cancer and 638 patients with hypopharyngeal cancer were included in the analysis. For advanced hypopharyngeal cancer (stage III and IVa), the overall survival and disease-free survival in patients receiving primary surgery with or without radiotherapy were statistically better than the matched sample who received chemoradiotherapy. For oropharyngeal cancer, the survival benefit only existed in stage IVa patients who received primary surgery with or without radiotherapy.

Conclusions: The study showed that primary surgery with or without radiotherapy might have survival benefit in patients advanced oropharyngeal or hypopharyngeal cancer as compared to chemoradiotherapy.

Legal entity responsible for the study: Koo Foundation Sun-yat Sen Cancer Center

Funding: Health and Welfare Surcharge of Tobacco Products grant of Taiwan

Disclosure: The author has declared no conflicts of interest.

1070P Comparison of carboplatin with 5-fluorouracil (carbo-5FU) versus cisplatin as concomitant chemoradiotherapy (CRT) for locally advanced head and neck squamous cell carcinoma (LA-HNSCC)

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Background: CRT including three cycles of cisplatin is considered the standard of care for LA-HNSCC. Around one third of the patients cannot complete cisplatin due to toxicity. Carbo-5FU can be used as an alternative. The aim of this study was to compare tolerability and efficacy between CRT with carbo-5FU and cisplatin.

Methods: This is a retrospective analysis of patients with LA-HNSCC treated with concomitant CRT in two Dutch cancer centers between 2007-2016. All patients received intensity modulated radiotherapy. One center routinely administered carboplatin 300-350 mg/m^2 at day 1, 22 and 43 followed by 5FU 600mg/m^2/day for 96 hours. The other center used cisplatin 100 mg/m^2 at day 1, 22 and 43. Primary endpoint was chemotherapy completion rate. Secondary endpoints included: reason for discontinuation, number of unplanned admissions, overall survival (OS) and disease free survival (DFS). Associations between clinicopathological parameters and OS were determined with multivariate Cox regression analyses.

Results: In the carbo-5FU cohort (n = 190), 61.6% of the patients completed chemotherapy versus 76.7% (p = 0.001) of the patients in the cisplatin cohort (n = 223). Discontinuation caused by chemotherapy specific toxicity occurred twice as often in the carbo-5FU cohort (odds ratio 2.2, 95%CI, 1.38-3.5). Patients in the cisplatin cohort were more likely to have an unplanned admission (OR 2.96, 95%CI, 2.21-4.27). The risk of death was higher in the carbo-5FU cohort (HR 1.50, 95%CI, 1.06-2.12, p = 0.02) with a three-year OS of 64.6% compared to 76.6% in the cisplatin cohort. Similar results were observed for DFS (HR 1.39, 95%CI, 0.99-1.93, p = 0.06). T-classification, N-classification, smoking and p16 status were independently associated with OS, but chemotherapy regimen was not (HR 1.04, 95%CI, 0.72-1.51, p = 0.84).

Conclusions: Patients treated with carbo-5FU less frequently completed chemotherapy because of chemotherapy specific toxicity. Better OS was observed in the cisplatin cohort, but chemotherapy regimen was not independently associated with OS.

Legal entity responsible for the study: S.F.Oosting

Funding: None

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1071P Postoperative radiotherapy with weekly cisplatin in locally advanced head and neck cancer

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Background: The aim of this study is to analyze the results of over 10 years experience with postoperative radiochemotherapy in patients diagnosed of locally advanced squamous cell carcinoma of head and neck based in cisplatin 40mg/m2/week.

Methods: From March 2004 to August 2015, 104 patients were treated in our department. All patients received chemoradiation therapy with adjuvant intent based in the same scheme: radiotherapy 50 Gy to clinical target volume (CTV) and 66-70 Gy to areas with close margin or extracapsular lymph node involvement and weekly cisplatin at 40mg/m2 concomitant to radiotherapy.

Results: The median age was 59 years (range 36-76), 85 patients were male (81.7%) and 19 were female (18.3%). The pathological stage was: 2.9 stage II, 8.7% stage III and 88.4% stage IV. Locations: 38.5% larynx, 38.5% oral cavity, 17.3% oropharynx, and 5.8% hypopharynx. 76.2% of patients received at least 5 cycles of chemotherapy. G3 toxicity was observed in 33% of patients being mucositis and epitelitis the most frecuents. G4 toxicity was not detected in any patient. Median follow-up was 81 months (range 18-137). Two-year and five-year overall survival (OS) were 90% and 76% respectively and disease-free survival (DFS) were 69.07% and 52.57% respectively. In multivariate analysis two or more positive nodes and longer time between surgery and

onset of radiotherapy were significant predictors of poorer OS and extracapsular extension, positive margin and longer time between surgery and onset of radiotherapy were significant predictors of poorer DFS.

Conclusions: In our serie, postoperative radiochemotherapy based in weekly cisplatin at 40mg/m2 in patients diagnosed of locally advanced squamous cell carcinoma of head and neck offers a good toxicity profile and results comparable to those published in the literature with 3-weekly cisplatin scheme. The number of positive nodes, longer time between surgery and onset of radiotherapy, extracapsular extension and positive margin were desfavorable prognostic factor related with SLE and OS in the multivariate analysis.

Legal entity responsible for the study: Hospital Ramón y Cajal

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1072P Effectiveness and toxicities of cetuximab in combination with concurrent chemoradiotherapy in locoregionally advanced nasopharyngeal carcinoma: A propensity score-matched analysis

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Background: There is increasing evidence showing that concurrent chemoradiotherapy (CCRT) may be inadequate for patients with locoregionally advanced nasopharyngeal carcinoma. Until now, no randomized controlled clinical trial has proved the effectiveness of cetuximab plus CCRT.

Methods: There were 681 consecutive stage III-IVB NPC were included in this retrospective study.75 underwent CCRT with cetuximab and 606 received CCRT.The nasopharyngeal and neck tumor of all patients were treated by intensity modulation radiated therapy (IMRT).

Results: After matching at a 1:2 ratio, 150 patients were treated with CCRT and 75 with CCRT plus C were selected. The 3-year PFS rates (83.7% vs 72.0%, P = 0.036) and 3-year LRFS rates (98.6% vs 90.2%, P = 0.034) were higher for patients in the CCRT plus C arm than with CCRT alone. Furthermore, a marginal trend of increasing risk of 3-year DMFS rates (83.9% vs 78.4%, P = 0.301) and 3-year OS rates (91.2% vs 85.8%, P = 0.123) was found. The results indicated that CCRT plus C treatment was a significant and independent protective predictor for 3-year PFS (P = 0.015) and LRFS rates(P = 0.047). When focusing on stage T4 and/or N3 in the subgroup, the CCRT plus C arm achieved significantly prolonged 3-year PFS (79.9% vs 62.6%, P = 0.022) and a marginally increased OS (88.0% vs 77.9%, P = 0.086) compared with that of CCRT alone. Additionally, the 3-year LRFS (97.0% vs 90.9%, P = 0.246) and DMFS (79.9% vs 67.8%, P = 0.161) were enhanced in patients with CCRT plus C compared to CCRT alone. When concentrating on stage III patients, there were no considerable statistically significant differences found in 3-year PFS, OS, LRFS, and DMFS rates between patients with and without cetuximab. No significant difference was observed in the late toxicities between the two treatments.

Conclusions: This propensity-matched study reveals that patients with T4 and/or N3 stage could benefit from the combination of cetuximab with the current chemoradiotherapy in locoregionally advanced NPC, although with more acute moderate to severe toxicities. However, this strategy remains to be validated in a prospective randomized controlled study.

Clinical trial identification: This retrospective study has no clinical trial identification.

Legal entity responsible for the study: Department of Radiation Oncology Nanjing Medical University Affiliated Cancer Hospital, Jiangsu Cancer Hospital, Jiangsu Institute of Cancer Research

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Disclosure: All authors have declared no conflicts of interest.

1073P Safety and efficacy of nimotuzumab with concurrent chemoradiotherapy in unresectable locally advanced squamous cell carcinoma of head and neck: Indian rural hospital experience

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Background: The aim of this study was to evaluate the safety and efficacy of nimotuzumab, a humanized monoclonal antibody against epidermal growth factor receptor, in combination with chemoradiation for head and neck squamous cell cancer (HNC).

Methods: The hospital data of 42 patients with HNC who were treated with nimotuzumab from January 2012 to December 2016 were evaluated. Three patients who had undergone prior surgery were excluded and 39 patients diagnosed with locally advanced (stage III- IVb) unresectable HNC who were treated with concurrent chemoradiotherapy with weekly nimotuzumab were considered for final analysis. Tumour response was calculated as per RECIST criteria 1.1. Subgroup analysis was performed to assess association of tumour response with independent variables such as age, gender, histopathological grades and TNM stages using chi square or Fischer exact test. Overall survival (OS) and progression free survival (PFS) was calculated from date of diagnosis using Kaplan-Meier method. All patients were assessed for toxicity and adverse events (AE) were reported as per common terminology criteria for AE v 4.0. Statistical analysis was done using SPSS software (v19.0).

Results: At 24 weeks after completion of treatment, objective response rate (complete response [CR] + partial response [PR]) was 97.44% with 26 (66.67%) patients showing CR, 12 (30.77%) patients with PR and one patient (2.56%) had stable disease. Subgroup analysis did not show significant association of tumour response, although men, patients older than 65 years, laryngeal cancer, tumour grade III, TNM stage III showed more complete responses. OS at one year and two years was 100% and 72.9%, while PFS at one year and two years was 87% and 54.40%, respectively. Incidence of grade I, II, III and IV toxicity was 30%, 18.18%, 41.82%, 10%, respectively. No grade V toxicity was observed. Common AE observed were neutropenia (20.91%), mucositis (33.64%), vomiting (18.18%), diarrhea (2.73%), skin reaction (24.55%). Nimotuzumab was observed to be safe with no additional adverse events (hypersensitivity, allergic reaction and skin changes) were reported during the study period.

Conclusions: Nimotuzumab is an efficacious and safe option when added to concurrent chemoradiotherapy in patients with locally advanced Head and Neck cancer.

Clinical trial identification: 125/12

Legal entity responsible for the study: Dr. Shyamji Rawat

Funding: None

Disclosure: D. Pawar: Works in a Pharmaceutical company. S. Chaudhari: works for Pharmaceutical company. All other authors have declared no conflicts of interest.

1074P A phase II study of combination chemotherapy with cetuximab/S-1/low dose cisplatin as neoadjuvant manner for oral squamous cell carcinoma patients

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Background: In oral cancer therapy, functional preservation, as well as survival, is a very important matter to consider. One of the methods for organ preservation is an effective preoperative (neoadjuvant) chemotherapy. We previously reported the good antitumor effect and good tolerance of low dose cisplatin/S-1 at ESMO 2004 and 2006. Cetuximab enhances the antitumor effect of cisplatin/5-Fluorouracil . We investigated the feasibility of combining cetuximab/low dose cisplatin/S-1 chemotherapy as a neoadjuvant regimen for patients with oral squamous cell carcinoma.

Methods: Consecutive patients (n = 14) with newly diagnosed stage II-IV oral squamous cell carcinoma were enrolled in this study from July 2014 to June 2016. Patients were administered S-1 80mg/m^2/day (day 1-14), cisplatin 5 mg/m^2/day (day 1-5,8-12) and cetuximab 400mg/m^2/day on day 1 and 250mg m^2/day on day 8. This was followed by definitive surgery. Clinical response was assessed by clinical findings and/or CT according to RECIST and histopathological effects were evaluated with surgical specimens.

Results: The rate of clinical response, including complete response (CR) and partial response (PR), was 85.7%: CR 21.8%, PR 64.3%, SD (stable disease) 14.3%. The rate of histological response was 71.4%: CR 21.4%, PR 50%, no change 28.6%. Toxicities above grade 3 were neutropenia (7.1%), hypokalaemia (7.1%), leukocytopenia (7.1%), thrombocytopenia (7.1%), anorexia (21.4%), diarrhoea (7.1%) and nausea (7.1%). Most toxicities disappeared within 8 weeks after chemotherapy. No serious adverse effects were observed in the majority of patients. Conservative surgery was applied to 12 patients, except 2 patients with SD and 5 of 9 patients who needed reconstruction were able to avoid reconstructive surgery.

Conclusions: Combination chemotherapy with cetuximab/low dose cisplatin/S-1 represents an effective antitumor therapy with mild to moderate toxicities. It is suggested that this regimen is superior to low dose cisplatin/S-1 and can promote function preserving surgery.

Clinical trial identification: UMIN000014632

Legal entity responsible for the study: Individual person

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1075P Role of induction chemotherapy in locally advanced T4b oral cavity cancers: A single Institute experience

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Background: The standard of care for oral squamous cell carcinoma (OSCC) at present, consist of surgical resection followed by adjuvant radiotherapy and chemotherapy as indicated. However, indications of induction chemotherapy (IC) in oral cancers are not clearly defined. This retrospective analysis aimed to investigate the efficacy, toxicity and impact of induction chemotherapy in locally advanced T4b oral cavity squamous cell cancers.

Methods: Patients diagnosed with locally advanced T4b OSCC from January 2013 and March 2017 at our centre, who received 2-3 cycles of IC and then assessed for resectability, were reviewed retrospectively. Patients' profile, response and toxicity of IC, resectability status and overall survival (OS) were evaluated. Statistical analyses were done by SPSS version 17.0.

Results: Total 134 patients received IC, and out of them 98 (73.1%) were males. Median age at diagnosis was 44 years (range 31-60 years). 107 (79.8%) of our patients received doublet chemotherapy (with paclitaxel + cisplatin), and the rest of the patients received triplet regimen (with paclitaxel/docetaxel + cisplatin + 5-FU). Majority of the patients had buccal mucosa cancers (n = 92), followed by gingivo-buccal sulcus (n = 26) and oral tongue (n = 16) primaries. After IC, partial response was achieved in 25 (18.7%) patients, stable disease in 83 (61.9%) patients and disease progression was noted in 26 (19.4%) patients. Post-induction chemotherapy, resectability was achieved in 28 (21%) of 134 patients, but 8 of them did not undergo surgery due to logistic and personal reasons. The median OS of patients who underwent surgery followed by adjuvant local therapy (n = 20) was 18.7 months (95% CI: 16.2-21.5 months) and for those treated with non-surgical local therapy (n = 114) was 7.9 months (95% CI: 6.2-9.2 months) (log-rank p = 0.000).

Conclusions: IC may improve the resectability in our patients with T4b OSCC with a manageable toxicity profile. Patients underwent resection had a significantly better median OS than those who received non-surgical local treatment.

Legal entity responsible for the study: Kidwai cancer institute

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1076P Concurrent chemoradiotherapy (CCRT) versus induction docetaxel, cisplatin and 5-fluorouracil (TPF) followed by CCRT in locally advanced hypopharyngeal and base of tongue cancer: A randomized phase II study

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Background: To date, clinical trials have not consistently supported the use of induction chemotherapy (IC) for locally advanced head and neck squamous cell cancer (LASCC). Hypopharyngx and base of tongue (BOT) cancer has shown relatively poor survival compared to other LASCC. We tried to investigate the role of IC for improvement over current chemoradiotherapy (CRT) in patients with locally advanced hypopharynx and BOT cancer.

Methods: Treatment-naïve patients with nonmetastatic stage III/IV hypopharyngeal or BOT cancer were randomly assigned to receive CRT alone (CRT arm: cisplatin 100mg/m^2 3-weekly for 2 times plus radiotherapy 68.4Gy/30fraction on weekday) versus two 21-day cycles of IC (docetaxel 75mg/m^2 on day 1, cisplatin 75mg/m^2 on day 1, and fluorouracil 750mg/m^2 on days 1 to 4) followed by same CRT regimen (IC arm). The primary endpoint was progression-free survival (PFS) and 90 patients are required to show the superiority of IC arm with one-sided alpha 0.1 and power of 0.85.

Results: This study closed early after enrollment of 36 patients (19 in CRT arm and 17 in IC arm) because of slow accrual. After a median follow up of 47.2 months, there was no significant difference in PFS: the median PFS were 26.8 months for CRT arm and not reached for IC arm (Hazard ratio: 0.55, 95% CI 0.19-1.60). However, the survival curves widely separated with a plateau after 3-years, suggesting the survival benefit from induction chemotherapy: 3-year PFS rates were 45% and 68%, and 3-year overall survival rates were 56% and 86% (HR: 0.35, 95% CI: 0.07-1.69), in CRT and IC arms, respectively. In both subgroups with BOT and hypopharyngeal cancer, survival outcomes of IC arm were also insignificantly superior to those of CRT arm. All adverse events were manageable and there was no grade 3/4 toxicity except one patient had Gr3 stomatitis in IC arm.

Conclusions: This study failed to demonstrate that induction TPF chemotherapy improves survival in patients with BOT and hypopharyngeal cancer, possibly due to small number of subjects. However, it suggested favorable outcome with induction chemotherapy, and further large randomized studies are needed to this population.

Clinical trial identification: NCT01312350

Legal entity responsible for the study: Samsung medical center

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1077P Do patients over 70 years with advanced head and neck squamous cell carcinoma tolerate curative intent concurrent chemo-radiation? Predictors of oncological outcomes

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Background: Survival benefit of adding chemotherapy to radiotherapy (RT) in patients (pts) age>70 yrs of head and neck squamous cell carcinoma (HNSCC) has not been found in literature. Our institutional policy is to offer concurrent chemoradiation (CCRT) to patients > 70 years with a good ECOG status.

Methods: Retrospective analysis of stage III/IV HNSCC in pts > 70 years who received linac based radical CCRT with dose equivalent to 70Gy in conventional fractionation (n = 57) between 2006 to 2014 were included.

Results: Pts with stage III/IV (25.6%/75.4%) HNSCC (n = 57) of oropharynx (n = 15), larynx (n = 18) or hypopharynx (n = 24) underwent radical CCRT having mean age 75.18 yrs (range 70-86 years) and male to female ratio of 10.4:1. Pts on CCRT who got cisplatin (CIS) (n = 35) and carboplatin(CARBO) (n = 22) had mean weight loss of 3.53 (range 0-10) kgs. 61.4% completed chemotherapy (defined as cumulative dose of 200mg/m2 of CIS and 5 weekly dose of CARBO at AUC 2) and 98.2% completed RT without any treatment related death. Higher grades of neutropenia (33.3%) and hyponatremia (17.5%) with CIS and hypercreatinemia (10.5%) with CARBO was noted. Tube dependence (gastrostomy/tracheostomy) had 2.7-fold increase in risk of death in pts (n = 25; 44%) with hypopharynx/larynx cancer, compared with stage and subsite matched pair analysis in pts < 60 years. Factors predicting good PFS were ECOG (1 vs 2) HR = 0.25 (95%CI:0.09-0.70), Completion of treatment without any breaks while on CCRT, HR = 2.54 (95%CI:1.02-6.32, p = 0.04), and age in 70-75 years, HR = 1.09 (adjusted for alcohol and smoking) (95%CI: 1.01-1.20, p = 0.08). Factors suggestive of poor PFS were hyponatremia, hypercreatinemia and weight loss > 3kgs from their baseline. PFS (80%) in pts with stage III and IV disease was 22 (95%CI: 12.4-87.2) months and 15.53 (95%CI: 8.6-20.6) months respectively.

Conclusions: Curative intent CCRT should be considered as standard of care in elderly patients > 70 years with good ECOG status. Both cisplatin and carboplatin showed significant benefit in PFS with fewer side effects. Aggressive swallowing rehabilitation, abstinence from smoking and alcohol are likely to improve outcomes.

Legal entity responsible for the study: Amrita Institute of Medical Sciences

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1078P Multidisciplinary team management in head and neck cancer: The real life experience

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Background: Multidisciplinary team (MDT) management in oncology is integrated in a legal framework in France. This practice is essential in Head and Neck cancer management with its complex and multimodal treatments. Some trials report a positive impact of MDT on overall survival of advanced head and neck cancers. The objective of this study was to report the experience of MDT management in Head and Neck Cancer in the Lucien Neuwirth Cancer Institute over the past 6 years.

Methods: Records from bi-monthly MDT meeting from 2010 to 2015 were selected for this study. Number of medical cases and type of present medical specialists were noticed. Data from MDT records were reported: clinical characteristics (performans status, weight), anatomical localisation, TNM and pathological classification, and the treatment plan decision. Impact of MDT meeting on treatment delay was also analysed.

Results: As of December 2015, 1848 clinical cases were discussed with 1786 patients and 138 MDT meetings. Majority of patients were discussed only once in meeting, and 3% (52) patients were discussed twice. An average of 16 patient's cases were discussed per-meeting. 1368 patients (74.1%) were presented at primo-diagnosis status and 481 (25.9%) in a recurrence status. 81% of patients were at stage III or IV. 969 (52.4%) patients had a treatment before MDT. Surgery (73.2%) was the main treatment operated before meeting. Radiation therapy delay after MDT was 9.8 days for dosimetric planification CT and 21 days for first radiation treatment session.

Conclusions: The percentage of presented recurrent patients is reasonable regarding epidemiologic data in head and neck location. MDT seems not delay radiation treatment occurring within 21 days after MDT. Unfortunately we underlighted a majority of patients surgically treated before MDT discussion.

Legal entity responsible for the study: Nicolas Magné
Funding: None
Disclosure: All authors have declared no conflicts of interest.

1079P Long-term response to second-line afatinib in patients with recurrent or metastatic head and neck squamous cell carcinoma (R/M HNSCC): Analysis of the LUX-Head & Neck 1 (LHN1) trial

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Background: In the Phase III LHN1 trial, second-line afatinib (A) significantly improved PFS (primary endpoint) vs methotrexate (MTX) in pts with R/M HNSCC. Tumour biomarker analyses have shown that survival benefit with A vs MTX was more pronounced in pts with p16/ErbB3-negative, EGFR-amplified, PTEN-positive disease. We present post-hoc analyses of A long-term responders (LTRs).

Methods: Pts with incurable R/M HNSCC who had received first-line platinum-based therapy were randomised to A (40mg/day) or MTX (40mg/m^2/week) and treated until progression/intolerable AE. LTRs were defined as pts treated with A $\geq$ 12 mos. Tumour biomarkers were assessed by IHC (p16, ErbB3, PTEN, cMET) and FISH (EGFR amplification); pre-treatment (tx) serum samples were analysed with the VeriStrat® (VS) test and classified as VS-Good/Poor.

Results: 11/322 (3%) pts treated with A were LTRs with a median (range) tx-duration of 16 (12−39) mos. All pts had stopped tx at analysis. Baseline characteristics in LTRs were similar to the overall dataset, except (LTRs/overall): oral cavity primary tumour site (45%/29%); M1 disease (45%/66%); previous therapy with EGFR-antibodies (18%/59%). Median OS was 18.1 mos; median PFS (central independent review) was 14.9 mos. ORR was 45% (CR: 18%; n = 2). The frequency of pts who received $\geq$1 subsequent therapy was similar to the overall dataset (LTRs, 45%; overall, 51%). In LTRs with available biomarker data, 3/3 (100%) pts were p16-negative, 4/4 (100%) pts were ErbB3-negative, 2/4 (50%) pts were PTEN-positive, 3/3 (100%) pts were cMET-positive, 2/3 (67%) pts had EGFR-amplification, and 5/5 (100%) pts were VS-Good. Tolerability-guided dose reductions were more frequent among LTRs (55% vs 32% overall).

Conclusions: In the LHN1 study, some platinum-pre-treated pts with R/M HNSCC derived a long-term survival benefit from A; median OS was ~1.5 yrs and >11 mos longer than in the overall dataset. Limited biomarker data available in these LTRs suggests that p16/ErbB3-negativity and EGFR-amplification might be potential predictive biomarkers for long-term benefit from A; however, results were not conclusive due to small sample size.

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Legal entity responsible for the study: Boehringer Ingelheim
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1081P Benefit of cetuximab addition to a platinum-fluorouracil-based chemotherapy in an unselected population of metastatic head and neck cancer patients and effect of KRAS Lcs6 variation on cetuximab response

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Background: While the EXTREME protocol, including platinum (P) fluorouracil (FU) and cetuximab (Cx), is the gold-standard first line chemotherapy for metastatic head neck cancer patients (MHNC), its benefit in an unselected population has never been evaluated. Furthermore, KRAS Lcs6 variation was reported as a potential marker for greater efficacy of EGFR-targeted therapy. We investigated the benefit on progression-free survival (PFS) and overall survival (OS) of adding Cx to PFU as first line treatment for MHNC in an unselected population. We also assessed if there was a differential efficacy of Cx according to KRAS Lcs6 status.

Methods: This monocentric retrospective study included all the patients treated by at least two cycles of PFU+/-Cx between 2005 and 2014 as first line of palliative chemotherapy for MHNC. When tumor samples were available, the KRAS LCS6 variant status (rs61764370) was determined by pyrosequencing, and the p16 status by immuno-histo-chemistry.

Results: 134 patients were included: 59 (44%) treated with PFU and 75 (56%) with PFUCx. Baseline characteristics were comparable between the two groups. Of note 30% of the patients had a stage 2 or 3 performance status (PS). In univariate analysis, a longer median PFS was observed with PFUCx compared to PFU (6.1 vs 4.4 months respectively, HR 0.68, p = 0.02). Median OS were not different (11.1 months with PFUCx versus 9.1 with PFU, p = 0.2). Among the 110 tumor samples available, 29 (25%) had a KRAS-variant and 14 (12.7%) were p16 positive. No differences in OS nor PFS were observed according to the KRAS-variant status. When considering only the patients treated with PFUCx, presence of the KRAS-variant (n = 17) was not associated with a better response (p = 0.5). In a multivariate analysis including PS $\leq$ 1, addition of Cx, KRAS status, p16 status and age $\leq$ 55 as variables; addition of Cx to PFU was the only factor related to a better PFS (p = 0.008).

Conclusions: This retrospective study confirmed the effectiveness of the EXTREME protocol on PFS in an unselected population of MHNC patients. KRAS LCS6 variant was not related to a differential response to Cetuximab in MHNC population.

Legal entity responsible for the study: Centre Henri Becquerel
Funding: IRON - Centre Henri Becquerel
Disclosure: All authors have declared no conflicts of interest.

1082P A pilot study of apatinib in heavily pretreated metastatic adenocarcinoma of the head and neck

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Background: Although antiangiogenic therapy is effiective in advanced lung, breast, renal, hepatic, and colon cancers, limited is known about its value in the cancer of the Head and Neck. Apatinib is an oral, highly potent tyrosine kinase inhibitor targeting vascular endothelial growth factor receptor 2 (VEGFR-2). This prospective phase II study (NCT02989259) aims to investigate the efficacy and safety of apatinib in heavily pretreated patients (pts) with metastatic adenocarcinoma of the Head and Neck.

Methods: This study enrolled pts with metastatic adenocarcinoma of the Head and Neck, who failed in the metastatic setting at least one prior chemotherapy regimen. The primary end point of this study was progression free survival (PFS). Secondary end points included objective response rate (ORR), disease control rate (DCR), overall survival (OS), and safety. Patients were treated with apatinib 500 mg daily. Efficacy was assessed every 6 weeks.

Results: From December 2016, we recruited 10 pts, including 8 males and 2 females, with a median age of 53 years (26-71). Median number of previous chemotherapy regimens for the metastatic diseases was 2 (1-3). Median follow-up time was 4.3 months. 8 pts were eligible for efficacy analysis. ORR was 25% (2/8). DCR was 87.5% (7/8). Median PFS and median OS were not reached. The most common adverse events (AEs) of all grade were hypertension (n = 5), nausea (n = 4), fatigue (n = 4) and hand-foot syndrome (n = 3). The most common grade 3/4 AEs were hypertension (n = 2), thrombocytopenia (n = 1) and oral mucositis (n = 1). Toxicities were tolerable and manageable.

Conclusions: Our results so far indicated that apatinib exhibited objective efficacy in heavily pretreated, metastatic adenocarcinoma of the Head and Neck with acceptable safety.

Clinical trial identification: the trial protocol number: NCT02989259 release date: December 2016

Legal entity responsible for the study: The Institutional Review Board of the Cancer Institute/Hospital, CAMS & PUMC Institutional Review Board of the Cancer Institute/Hospital, CAMS & PUMC

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1083P Natural history and prognostic factors of head and neck cancer patients with bone metastases: A retrospective Italian study

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Background: We performed a retrospective survey to study the natural history and the prognostic factors of patients (pts) with bone metastases (BMs) from head and neck cancers (HNCs).

Methods: Clinical records of pts treated at 11 oncologic centers across Italy were retrieved. All pts were selected on the base of BMs either at diagnosis or at subsequent time points. Pts with a diagnosis of nasopharyngeal carcinoma (NPC) were analyzed separately. The time-to-first bone metastasis was calculated from initial diagnosis. The skeletal-related events (SREs) (fractures, medullary compression, hypercalcemia) were recorded from the date of BMs diagnosis.

Results: From 2008 to 2016, 192 HNC pts with BMs (64 NPCs and 128 other-HNCs) were collected. Median time to first BM was 9 and 12 months for NPCs and other-HNCs, respectively. SREs occurred in 9% and 27% NPC and other-HNC pts, respectively. Pts received specific antineoplastic treatments (92%) or best supportive care (8%). Median progression free survival (PFS) and overall survival (OS) were 11 and 25 months in NPC-BM pts and only 5 and 6 months in other-HNC-BM pts, respectively. SRE did not affect the pt prognosis except for hypercalcemia that was associated with a poorer prognosis (not significant). Biphosphonates and/or denosumab were administered in 34% NPC and 33% other-HNC pts, respectively. The administration of bone-directed therapies, also including radiation therapy and surgery on BMs, was associated with a better survival at univariate analysis in both NPC and other-HNC (Hazard Ratio [HR]: 0.43, 95% confidence interval [CI] .008-.237, p <.0005 in NPC and HR 0.37, 95% CI: .191-.735, p .004 in other HNC, respectively).

Conclusions: In HNC pts destined to develop BMs, these events occur early in the natural history of these diseases. The onset of BMs predicts a poor survival in non-NPC HNC pts. SREs are more frequent in non-NPC HNC pts. Bone directed therapies are correlated with better outcome.

Clinical trial identification: Id NP1848 - Study SURMOS - Release date: 11 Dec 2014

Legal entity responsible for the study: Department of Medical and Surgical Specialties, Radiological Sciences and Public Health, University of Brescia, Spedali Civili Hospital, Medical Oncology Unit, Brescia, Italy

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1084P Prognostic impact of the neutrophil-to-lymphocyte ratio (NLR) on overall survival in patients treated with chemoradiotherapy for head and neck cancer

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Background: The neutrophil-to-lymphocyte ratio (NLR), a marker of the systemic inflammatory response, has been reported to have prognostic value in different cancer settings. In this study we aimed to assess the prognostic impact of NLR in a cohort of patients with head and neck cancers.

Methods: Patients with head and neck cancer treated with concurrent chemo-radiotherapy (Cisplatin) between 01/2013 and 12/2015 were included in this study. NLR was analyzed as a continuous variable and as dichotomous variable (≤ 5 vs. > 5). The primary end point was overall survival (OS). Progression free survival (PFS) was the secondary endpoint. Univariate analysis was used to identify associations and to select variables included in multivariate Cox regression analysis to determine prognostic value.

Results: 146 patients (132 squamous cell carcinomas (SCC), 10 undifferencied nasopharyngeal carcinomas (UCNT) and 4 neuroendocrine carcinomas) were included in this analysis. The median follow up was 20.6 months (2.4-37.0 months). 1-year and 2-year OS were 87.1% and 82.3%, respectively.1-year and 2-year PFS were 75.9% and 68.0%, respectively. On univariate analysis, OS significantly differed between groups NLR ≤ 5 vs. > 5. In the overall population (OP) (HR: 2.6; IC95%: [1,05-6,53]; $p = 0036$) and in non-oropharyngeal subpopulation (HR: 3.67; IC95%: [1,19-11,4]; $p = 0,016$) but not in the oropharyngeal subpopulation ($p = 0,51$). In multivariate analysis NLR >5 was significantly associated with a poorer OS in the OP (HR: 2.89; IC95%: [1,14-7,33]; $p = 0.025$) and in non-oropharyngeal subpopulation (HR: 4.53; IC95%: [1,34-13,5]; $p = 0.014$). Body Mass Index (BMI) <18.5kg/m2 and poor performans status (PS: 1-2 vs 0) were also significantly associated with a shortened OS ($p = 0.010$ and 0.021, respectively). Only the BMI was found to be significantly associated with PFS ($p = 0.006$) in the OP.

Conclusions: In this cohort of patients treated with chemo-radiotherapy for head and neck cancer, pre-treatment NLR >5 was predictive of shorter overall survival. Further prospective clinical investigations are required to confirm these results and determine the clinical applicability as prognostic factor.

Legal entity responsible for the study: Centre Oscar Lambret

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Disclosure: All authors have declared no conflicts of interest.

1085P Association of ERP29 genetic polymorphism in microRNA-binding site with oropharynx cancer risk and prognosis

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Background: Our previous large-scale genotyping study identified more than 6,000 single nucleotide polymorphisms (SNPs) associated with base of tongue (BT) squamous cell carcinoma (SCC) risk in 49 patients and 49 controls. The SNP c.*293A>G of the ERP29, a tumor-suppressor chaperone, was selected for further analyses. An in silico analysis showed that microRNA (miR)-4421 shared binding site with 3'-untranslated region of variant allele of referred SNP while wild-type allele disrupt this target site. However, the role of this SNP in the risk and prognosis of oropharynx SCC (OPSCC) patients is still unknown. We aimed to verify whether the distinct genotypes or ERP29 c.*293A>G SNP influence the OPSCC risk and prognosis, and the ERP29 and miR-4421 expressions.

Methods: DNA from 250 OPSCC patients and 250 controls was analyzed by RT-PCR. The patients were treated with surgery, radiotherapy and/or platinum based agents. The ERP29 and miR-4421 levels were evaluated by qPCR using RNA of 58 controls. The differences between groups were calculated by chi-square, logistic regression model and Mann-Whitney tests. Progression-free survival (PFS) and overall survival (OS) times were calculated by Kaplan-Meier and Cox regression methods.

Results: ERP29 variant GG genotype was more common in OPSCC patients than in controls (6.4% vs. 3.6%, $P = 0.002$). Individuals with GG genotype were under 8.86-fold increased risk of OPSCC than others (95% CI: 2.20-35.69). Considering only the BTSCC patients, at 36 months of follow-up, shorter PFS were seen in patients with variant GG genotype (0.0% vs. 39.1%, $P = 0.01$, Cox: HR: 2.68, 95% CI: 1.21-5.95, $P = 0.01$). Individuals with ERP29 wild-type genotype showed higher levels of ERP29 mRNA when compared to others (1.44 vs. 1.10 arbitrary units AUs, $P = 0.005$). In addition, lower miR-4421 expression was observed in individuals with ERP29 AA genotype when compared to those with AG or GG genotypes (0.42 vs. 0.73 AUs, $P = 0.05$).

Conclusions: Our data present, for the first time, that *ERP29* c.*293A>G SNP is associated with increased risk of OPSCC and with worst survival of BTSCC patients, possibly due to variation of *ERP29* mRNA levels modulated by miR-4421.

Legal entity responsible for the study: University of Campinas

Funding: São Paulo Research Foundation (FAPESP) and Coordination for the Improvement of Higher Education Personnel (CAPES)

Disclosure: All authors have declared no conflicts of interest.

1086P Diagnostic and prognostic impact of plasma osteopontin in nasopharyngeal carcinoma

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Background: We investigated the diagnostic and prognostic impact of plasma osteopontin (pOPN) concentrations in advanced nasopharyngeal carcinoma (NPC).

Methods: Pre-treatment plasma samples from 138 patients with previously untreated and biopsy-proven NPC were collected. Plasma samples from another 70 healthy volunteer were served as control. OPN concentrations were measured by the enzyme-linked immunosorbent assay (ELISA). The patient characteristics were- age range 24-83 and median 48 years, male/female=97/41, WHO pathology type I/II/III=1/105/32, stage III/IV(M0)/IVC(M1) = 57/73/8. The treatment consisted of radiotherapy alone (2), concurrent chemoradiotherapy (28), and neoadjuvant chemotherapy plus radiotherapy (100) for M0 patients, and systemic chemotherapy with or without radiotherapy for M1 patients (8).

Results: NPC patients (median 97.2 ng/mL; interquartile range 72.1-130.4) had significantly higher pOPN level than normal control (median 61.6 copies/ml; interquartile range 44.9-88.1), $P<0.0001$. The area under ROC curve is 0.754, $P=0.0001$. The median concentrations of stage III, IV(M0), and IV(M1) were 85.4, 104.2, and 217.7 ng/mL respectively ($P=0.0002$). We divided patients into two groups by pretreatment pOPN concentration and found that patients with higher pOPN (>100 ng/mL) correlated with some clinically poor prognostic factors, such as older age, male gender, advanced T-stage, and advanced overall stage. Pretreatment pOPN affected patients' survival as well as rates of distant failure. The 5-year overall survival (56.6% vs. 81.4%, $P=0.0036$) and metastasis-free survival (66.3% vs. 81.2%, $P=0.0726$) were significantly lower in patients with pretreatment pOPN > 100 ng/mL than in those with pOPN < 100 ng/mL.

Conclusions: Pretreatment pOPN levels can serve as a useful diagnostic and prognostic marker for advanced NPC.

Legal entity responsible for the study: Taichung Veteran General Hospital

Funding: Taichung Veteran General Hospital

Disclosure: All authors have declared no conflicts of interest.

1087P Head and neck cancer (HNC) and synchronic lung cancer: Impact of the lung cancer on the management and prognosis of these patients. Data from the SYNCHRON GFPC 15-04 Study

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Background: Management of synchronous head and neck and lung cancer is almost difficult. The aim of this observational study was to describe the impact of the lung cancer on the management and prognosis of HNC.

Methods: Inclusion criteria were: consecutive patients diagnosed between January 2011 and December 2015 in 19 French centers with HNC and synchronous lung cancer (all stages). We describe: clinical characteristics, management and outcomes. Patient characteristics and treatment information was analyzed descriptively. Kaplan-Meier estimation was used to assess median overall survival.

Results: The study included 132 patients: men: 83%; 63,7 years old, current smokers: 59,8%; performans status: 0 and 1 for 22% and 66% of the patients respectively; high rate of comorbidities: cardiovascular: 63%, COPD: 33%. Main histology for HNC was squamous: 98%, (in oral cavity: 24%, oropharyngeal: 26%, hypo-pharyngeal: 22% and laryngeal: 28%) T classification was T1, T2, T3 and T4 in 16%, 24%, 28% and 18% of cases respectively, and N classification was N0, N1, N2, N3, for 36%, 18%, 20% and 8% of cases respectively. The main treatment was surgery, 37,1%, and chemo-radiotherapy, 35,6%. The diagnosis of lung cancer impacts the HNC management in 38% of the cases. Median delay between HNC and first day treatment was 54 days. HNC progressive free survival rate was 68% at 2 years. Lung cancers were mostly localized (stages I: 46%, stages II: 10%), squamous: 39%, or adenocarcinomas: 39%. Main treatments were surgery: 29%, mainly lobectomy, radiotherapy: 13%, radio-chemotherapy: 14% and chemotherapy alone: 35%. Seven patients didn't receive active treatment. Median delay of treatment was 82,3 days. Lung cancer progressive free survival rate was 35% at 2 years. OS was 40% at 2 years, better for stage I - II lung cancers (55%).

Conclusions: Synchronous lung cancer at HNC diagnosis significantly impacts the management and outcomes of HNC. Specific recommendations and multidisciplinary approach should be elaborate to improve the management of these patients.

Legal entity responsible for the study: Groupe Français de Pneumo-cancérologie

Funding: Boringer Pierre Fabre

Disclosure: All authors have declared no conflicts of interest.

1088P An estimation of the population survival benefit of first-course chemotherapy for head and neck cancers

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Background: Randomised clinical trials describe the benefit of chemotherapy for specific head and neck patients with selected patient and tumour characteristics. This study estimates the overall survival benefit of chemotherapy above all other modalities for the whole population of head and neck cancer patients in Australia, if evidence-guidelines were followed.

Methods: Decision trees with evidence-based indications for chemotherapy have been previously defined. For all defined indications, the highest level of clinical evidence available was identified. Multiple electronic citation databases were systematically queried, including Medline and Cochrane library. The benefits of first-course chemotherapy were estimated for 1-year and 5-year overall survivals. To assess the robustness of our estimates, univariate and multivariate analyses were performed.

Results: The estimated 1-year and 5-year absolute population-based survival benefits of optimally utilised chemotherapy for head and neck cancer patients in Australia are 5.5% (95% Confidence Interval, CI, 4.5%-6.8%) and 4.2% (95% CI, 3.6%-5.0%), respectively.

Conclusions: First-course chemotherapy improved population-based survival in head and neck cancer patients, when used in accordence with guidelines recommendations. Measurement of population survival benefits of cancer treatment is important as these can provide salient inputs for economic analyses, aid in priority setting in cancer program and guide quality improvement according to evidence-based guidelines.

Legal entity responsible for the study: CCORE, Ingham Institute for Applied Medical Research, Sydney, Australia.

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Disclosure: All authors have declared no conflicts of interest.

1089P GSTP1 c.313A>G, XPD c.934G>A, XPF c.2505T>C and CASP9 c.-1339A>G polymorphisms and severity of vomiting in head and neck cancer patients treated with cisplatin chemoradiation

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Background: Cisplatin (CDDP) chemotherapy associated with radiation (RT) has been used in head and neck squamous cell carcinoma (HNSCC) patients, and vomiting is a common side effect during treatment. This prospective study aimed to identify the roles of *GSTM1* and *GSTT1* (presents or nulls), *GSTP1* c.313A>G, *XPC* c.2815A>C, *XPD* c.934G>A and c.2251A>C, *XPF* c.2505T>C, *ERCC1* c.354C>T, *MLH1* c.−93G>A, *MSH2* c.211 + 9C>G, *MSH3* c.3133G>A, *EXO1* c.1765G>A, *TP53* c.215G>C, *CASP3* c.-1191A>G and c.-1168G>T, *CASP9* c.-1339A>G, *CASP8* c.-937_-932delAGTAAG, *FAS* c.-1378G>A and c.-671A>G, and *FASL* c.-157-687C>T single nucleotide polymorphisms, involved in CDDP metabolism, in vomiting severity in HNSCC patients treated with CDDP and RT.

Methods: We evaluated 88 HNSCC patients diagnosed June 2011-February 2014 which receive CDDP chemoradiation. Ondansetron and dexamethasone were administered as antiemetic therapy and evaluated using National Cancer Institute criteria. Genotypes were analyzed in genomic DNA by polymerase chain reaction based methods. The logistic regression model was used to identify variables influencing toxicities and significant results were validated using a bootstrap (bt) resampling to investigate the stability of risk estimates (1000 replications).

Results: GSTP1 c.313AG or GG genotype alone (46.7% vs 18.6%, P = 0.004) and combined with XPD c.934GA or AA (50.0% vs 16.7%, P = 0.02; P_{bt}= 0.008), XPF c.2505TC or CC (52.2% vs 16.7%, P = 0.02; P_{bt}= 0.007) and CASP9 c.-1339AG or GG (51.9% vs 16.7%, P = 0.02; P_{bt}= 0.01) genotypes were more common in patients with moderate/severe vomiting than other genotypes. Carries with GSTP1 c.313AG or GG genotypes alone and combined with XPD c.934GA or AA, XPF c.2505TC or CC and CASP9 c.-1339AG or GG genotypes had 4.28, 5.00, 5.45, and 5.38 more chances of presenting moderate/severe vomiting than others.

Conclusions: Our data suggest, for the first time, that inherited abnormalities in DNA repair and apoptosis pathways are capable of modulating emesis in HNSCC patients under CDDP chemoradiation, and may be used for selecting patients who deserve to receive distinct doses of antiemetics or association of potent antiemetics in clinical practice.

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Disclosure: All authors have declared no conflicts of interest.

1090P Analysis of the impact of the tumours committee on the multidisciplinary approach to head and neck epidermoid cancer in our institution

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Background: The objectives are to define the characteristics of people with HNSCC treated in our area and quantify the impact of the committee on the staging, the change in the initial treatment proposed to determine whether the selection of treatment by the multidisciplinary team (MDT) influences therapeutic compliance.

Methods: Observational retrospective study of two cohorts, which aims to analyse the variables in the cohort of patients handled by an MDT with respect to the patients without an MDT. We included all patients with an initial diagnosis of HNSCC at our centre between 2005 and 2012. The MDT cohort comprised those from 01/01/2009 to 31/12/2012. With access to the Pathological Anatomy database, the records of the MDT, the archived and computerised medical history, we collected the endpoints related to the patient (age, sex, ECOG), the tumour (date of diagnosis, location, and TNM stage), the treatment (therapy selected, change in treatment, compliance, reason for default). Definitive sample consists of 408 patients. A descriptive analysis is given of the clinical characteristics of the sample, together with the comparative bivariate analysis of these characteristics in the cohorts.

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%, S and radiotherapy (RT) 14.7%, RT 10% and chemo-radiotherapy 9.8%. From our comparative analysis we want to highlight (C1 vs C2) change in stage 26 vs 19.7%, increase 1.5 vs 15.4%($p < 0.001$), change of treatment 34.5 vs 39.9% ($p < 0.001$), organ-preservation without surgery 3 vs 6.3% ($p < 0.001$) and therapeutic compliance 91 vs 92.3% ($p = 0.72$).

Conclusions: The population served in our area presents clinical characteristics similar to those of other series published in our and other countries. The MDT improved the staging of the tumour before treatment in a statistically significant way. The change in treatment is higher, so as to be statistically significant, when the therapeutic planning is addressed by an MDT. No statistically significant difference was observed in therapeutic compliance rates when treatment was decided by the MDT.

Legal entity responsible for the study: María José Martínez-Ortiz

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1091P Prognostic nutritional index (PNI) is an independent prognostic factor in locoregionally advanced squamous cell head and neck cancer (LAHNSCC)

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Background: There is increasing evidence that the presence of an ongoing systemic inflammation response and the nutritional status are a stage-independent predictor of poor outcome in cancer patients. This study aims to investigate association of the Prognostic Nutritional Index (PNI), a proposed marker of cancer-related inflammation and nutritional status, with survival in LAHNSCC patients (pts).

Methods: We included 137 LAHNSCC pts treated with induction chemotherapy (ICT) followed by concurrent chemoradiotherapy (CCRT) at Hospital La Fe (HFV) (n = 50) and Hospital Clínico (HCV) (n = 87) between 2011-2016; they were used as a training (HFV) and validation (HCV) set respectively. Demographic and clinical data were collected. All nutritional factors were measured within 5 days before ICT. PNI was calculated as: 10× serum albumin concentration (g/dL) + 0.005× lymphocyte count (number/mm2) in peripheral blood (Nozoe et al, 2010). Receiver operating characteristic (ROC) curve was used to determine the optimal cutoff for PNI in the HFV set. Cox regression models were used to investigate the association of PNI with OS.

Table: 1091P The Prognostic Nutritional Index (PNI): definition

Score	Definition	Meaning
0 points	PNI ≥ cutoff = PNI-high group	Normal nutritional status – Low risk
1 point	PNI < cutoff = PNI-low group	Moderate severe nutritional impairment - High Risk

Results: At baseline, HFV pts were younger with a median age of 54.5 (41-59 years) vs 60.6(43-77 years) and with less advanced stage (stage III 18.8 vs 20.5%; stage IVA: 78.1 vs 62.1%; stage IVB:3.1 vs 17.2%). The optimal cutoff established in the HFV set was 45. According to this cutoff, 10 pts (20%) in HFV set had a low PNI. In HFV set, OS at 12-months follow-up (FU) was 75% in PNI-high group vs 37.5% in PNI-low group ($P = 0.032$) with a Hazard ratio of (HR) of 2.84 (95%CI 1.04-7.78) in the multivariate analysis. In the HCV set, a low PNI was found in 23 (26.4%) out of 87 pts. OS at 12-months FU was 95% in PNI-high group and 45% in PNI-low group ($p = 0.007$) with a HR of 3.9 (95% CI 1.45-10.98) in the multivariate analysis.

Conclusions: PNI is a valuable prognostic marker in LAHNSCC associated with survival in pts treated with ICT followed by CCRT. PNI could be useful for stratification in future clinical trials.

Clinical trial identification: None

Legal entity responsible for the study: Gema Bruixola

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Disclosure: All authors have declared no conflicts of interest.

1092P CASP9 c.-1339A>G and CASP3 c.-1191A>G polymorphisms in susceptibility and outcome of head and neck squamous cell carcinoma

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Background: We analyzed herein the roles of *CASP9* c.-1339A>G (rs4645978) and *CASP3* c.-1191A>G (rs12108497) single nucleotide polymorphisms (SNPs) of intrinsic apoptosis pathway on risk and behavior of head and neck squamous cell carcinoma (HNSCC).

Methods: DNA of 350 HNSCC patients and 350 controls was analyzed by polymerase chain reaction method and enzymatic digestion for genotyping. Patients were treated according to the Institutional protocol, including surgery, radio and chemotherapy. The statistical analyses were realized using chi-square, logistic regression model, multifactor dimensionality reduction (MDR), Kaplan-Meier, and univariate and multivariate Cox analyses.

Results: *CASP3* c.-1191AG or GG genotype was more common in patients with overall HNSCC (63.4% *versus* 53.4%, $P = 0.013$), male patients with overall HNSCC (65.5% *versus* 53.4%, $P = 0.011$), patients with SCC of oral cavity (OCSCC) (68.0% *versus* 53.4%, $P = 0.02$) and SCC of pharynx (PSCC) (62.7% *versus* 53.4%, $P = 0.010$) than in controls; carriers of genotypes were under 2.15 and 2.34-fold increased risks of overall HNSCC, 2.75 and 2.67-fold increased risks of OCSCC and PSCC, respectively. Interactions of *CASP9* and *CASP3* SNPs and tobacco on HNSCC, OCSCC, PSCC, and laryngeal SCC risks were evident in study ($P < 0.01$). At 60 months of follow-up, event-free survival was worst in patients with *CASP9* c.-1339GG genotype (35.9% *versus* 45.1%, $P = 0.04$) compared to others (Kaplan-Meier estimates). Patients with *CASP9* c.-1339GG genotype and *CASP9* c.-1339GG plus *CASP3* c.-1191GG genotypes had 1.46 more chances of disease progression or relapse and 2.66 more chances of evolving to death in univariate and multivariate analyses, respectively.

Conclusions: We present, for the first time, preliminary evidence that inherited abnormalities in the intrinsic apoptosis pathway, related to *CASP9* c.-1339A>G and *CASP3* c.-1191A>G SNPs, are important determinants of HNSCC risk and outcome. **Financial support**: Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP).

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1093P Resource-stratification of national comprehensive cancer network (NCCN®) head and neck cancers guideline

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Background: Resource constraints in low- and middle- income countries (LMICs) often impede critical medical care. 65% of new cases of lip and oral cancer, and 76% of related deaths occur in LMICs, where patients lack access to standard diagnostic tests and/or treatment approaches. The development of resource-stratified clinical guidelines promotes access to critical diagnostic and treatment pathways in LMICs.

Methods: To address the unmet need in LMICs, a multi-disciplinary committee of NCCN Member Institution experts developed the NCCN Framework™ for Head and Neck Cancers: Lip and Oral. In the evidence-based, resource-stratified Guidelines, recommendations from the NCCN Guidelines for Head and Neck Cancers were assigned to specific resource levels, based on access to various interventions and importance in

achieving clinical outcomes. International experts reviewed the resource-stratified Guidelines to assess utility in LMICs and NCCN approved and published the finalized guidelines.

Results: The NCCN Framework for Head and Neck Cancers: Lip and Oral has four resource levels: Basic, Core, Enhanced, and Parent guideline. The Framework for Basic Resources identifies essential services required for minimal standard of care for improvement in outcome; the Core Resources lead to improved outcomes but are not cost prohibitive; the Enhanced Resources recommend additional services that may improve outcomes, but may be cost prohibitive in certain settings. For initial treatment of early stage cancer of the oral cavity (T1-2, N0) as an example, the Enhanced Framework recommends surgical resection and radiation therapy (RT), but not sentinel lymph node (SLN) biopsy, which is recommended in the NCCN parent Guidelines and requires more advanced resources. The Basic Framework recommends surgical resection as the only primary treatment option, since RT may not be available at this resource level.

Conclusions: The NCCN Framework for Head and Neck Cancers: Lip and Oral provide LMICs with a system to optimize care in limited resource settings, and a map to improve cancer care incrementally as resources become available. Use of this framework facilitates improved patient care in resource-constrained settings.

Legal entity responsible for the study: National Comprehensive Cancer Network

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1094P Long-term results of chemoradiotherapy for stage III nasopharyngeal carcinoma patients and risk grouping by pretreatment EBV viral load

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Background: No previous study reported the treatment outcome of stage III nasopharyngeal carcinoma (NPC) patients. The aim of this study is to investigate the long-term clinical outcome of stage III NPC patients and do risk grouping by plasma EBV DNA assay for future therapy improvement.

Methods: A total of 356 previously untreated, pathologically-proven NPC patients with stage III disease and available pretreatment plasma EBV DNA data were enrolled in this retrospective study. Initial definitive treatment consisted of concurrent chemoradiotherapy or induction chemotherapy plus radiotherapy. Eighty-four of 356 (23.6%) patients also received post-RT adjuvant chemotherapy. Patients with pretreatment EBV DNA $>$ 1000 copies/mL were defined as a high-risk subgroup (n = 106) and the remaining patients as a low-risk subgroup (n = 250).

Results: After a median follow-up of 90 months, there were 66 recurrences (18.5%) and 57 deaths (16.0%). The 5-year overall survival (OS), progression-free survival (PFS), distant metastasis failure-free survival (DMFFS), and locoregional failure-free survival (LRFFS) for all 356 patients were 88.4%, 83.9%, 90.5%, and 90.5%, respectively. Thirty-five of 105 (33.0%) high-risk patients developed tumor relapse later, whereas only 12.4% (31/250) low-risk patients had tumor relapse ($P < 0.0001$) Survival analysis revealed that the high-risk subgroup had significantly worse OS (5-year rate, 79.% vs. 92.8%, $P < 0.0001$), PFS (73.7% vs. 88.4%, $P < 0.0001$), DMFFS (80.2% vs. 95.0%, $P < 0.0001$), and LRFFS (85.6% vs. 92.6%, $P = 0.0045$) than those of the low-risk subgroup.

Conclusions: Long-term treatment results for Stage III NPC patients were good. Risk grouping identified a subgroup of patients with high pretreatment EBV DNA had a significantly higher relapse rates and worse survivals. Future trial should strengthen treatment intensity for these high-risk patients.

Legal entity responsible for the study: Taichung Veterans General Hospital

Funding: Taichung Veterans General Hospital

Disclosure: All authors have declared no conflicts of interest.

1095P Nasopharyngeal cancer in children: Long term results the experience of the university hospital of Sfax (Tunisia)

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Background: Nasopharyngeal carcinoma in children is frequent in Mediterranean area. We aimed to report our experience in the treatment of this entity.

Methods: We retrospectively review the records of 76 young patients (<21 years) presenting with nasopharyngeal cancer during the period 1993 -2015. Diagnosis was confirmed with histological study of the biopsy of nasopharynx. Initial work-up included nasofibroscopy, CT scan and/or MRI of the nasopharynx and neck, chest X-ray, abdominal ultrasonography and bone scan. TNM 2009 classification was used. Patients treated before 2009 were retrospectively reclassified. Metastatic patients were excluded. Patients had cisplatin based regimen chemotherapy (neoadjuvant, concomitant or both). Radiotherapy was delivered at the dose of 70 to 75 Gy targeting the nasopharynx and involved cervical nodes. Prophylacting dose up to 50 Gy was delivered to the remaining cervical areas. Survival was studied with Kaplan Meier test. Late toxicities were assessed according to SOMA-LENT and RTOG scales in patients with a minimal follow-up of 24 months.

Results: Mean age was 16 years (9 – 20). Sex-ratio was 1,1. Seventy two percent of patients (n = 55) had locally advanced tumor (T3 or T4). Cervical nodal involvement was seen in 95% of cases (n = 71). There were 52 cases (68%) of N2 or N3. Sixty-six patients had neoadjuvant chemotherapy, 10 had concomitant and 5 had both. Five patients had exclusive irradiation. Radiotherapy was monofractionated in 45 cases and bifractionated in the remaining cases. Acute toxicities were tolerable. Mean follow-up was 198 months (28- 289). One patient experienced a local failure. Twenty-six presented metastatic failures. Overall survival rate at 10 years is 67,4%. Disease free survival rate at 10 years is 66,7%. Xerostomia was the most frequent late toxicity (97%). Patients experienced endocrine troubles (hypothyroidism in 19%, amenorrhea in 13%), cerebral necrosis (5cases), osteoradionecrosis (10 cases) and secondary cancer (3 cases).

Conclusions: Pediatric nasopharyngeal carcinoma has good prognosis despite frequent locally advanced disease at presentation. Combining radiotherapy and chemotherapy is the standard of care. Late toxicities are often severe and affect the quality of life.

Legal entity responsible for the study: University Hospital of Sfax - Tunisia

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1098P Incidence and impact of DPD mutation on neoadjuvant chemotherapy in head and neck cancers

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Background: Dihydropyrimidine dehydrogenase (DPD) is an enzyme essential for metabolism of 5FU. The incidence of polymorphisms or mutation in variable across different ethnic populations. This study is first report highlighting the high incidence of DPYD mutation is seen in head and neck cancers in India.

Methods: Consecutive patients with head and neck cancer undergoing TPF neoadjuvant chemotherapy at our centre between May 2015 - December 2016 underwent DPD mutation analysis. The haematological toxicities consisting of neutropenia and thrombocytopenia while gastrointestinal toxicities consisting of mucositis and diarrhea were considered as 5FU related toxicities for this analysis. Toxicities were graded in accordance with CTCAE (Common terminology criteria for adverse events) version 4.03. DPYD mutation analysis by Sanger sequencing on ABI 3500 platform, for the most prevalent exonic regions {Exon 13 –c1627 A>G(DPYD*5) p1543V (ATA>GTA); Exon 14 – 1845 G>T; (E615D) missense mutation, Exon 14 splice variant G>A and Exon 18 (DPYD*6) pV7321) - c2194 G>A (GTT>ATT)}. Descriptive statistics was performed using SPSS version 16 and RStudio. Proportions with 95% CI were described. Fisher's exact test was performed to see the relationship between DPD mutation status and grade 3-5 adverse events.

Results: Consecutive 118 patients were included in this analysis. The median age was 45 years (IQR 37.25-54.00 years). The median cycles of TPF received were 2 (range 1-4). DPD mutation was seen in 29 patients (24.59%, 95%CI 16.94-32.23%). The mutations were seen in exon 18 in 17 patients (14.4%), exon 13 in 9 patients (7.6%) and in both exon 13 & 18 in 3 patients (2.5%). 100 patients were eligible for assessment of adverse events (84.7%). The rate of grade 3-5 haematological and gastrointestinal adverse events was 64% and 35% respectively. The rate of grade 3-5 haematological (88.5% versus 55.4%, p-0.002) and gastrointestinal adverse events (57.7% versus 27.0%) were higher in DPYD mutated cohort.

Conclusions: This study signifies the importance of ethnic difference in drug polymorphism and mutations. The impact of these adverse events in DPD mutated patients justifies doing a DPD mutation prior to subjecting patient to 5FU in head and neck cancer.

Legal entity responsible for the study: Tata Memorial Hospital Centre, Mumbai

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1099P Radiotherapy related xerostomia in head and neck oncology: A systematic review

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Background: Radiotherapy in the head and neck region can lead to salivary gland hypofunction and as a result dry mouth ensues. We have undertaken this systematic review and meta-analysis to estimate the effectiveness of available interventions for radiotherapy-induced xerostomia and hyposalivia.

Methods: A systematic review and meta-synthesis techniques were adopted to identify, appraise and synthesize the relevant literature regarding the experience of nutritional symptoms of HNC patients conducted according to the PRISMA guidelines. Several

electronic databases such as PubMed, CINAHL, Scopus, PsycINFO and the Cochrane Library databases were searched.

Results: 1598 patients from Eighteen studies were included in the systematic review. Cholinergic agonists like Pilocarpine, cevimeline and bethanechol were tested in most studies. Other drugs tested include malic acid, physostigmine, specific monoclonal antibodies like Rituximab, fluoroquinolones, saliva substitutes/mouthcare systems, hyperthermic humidification, acupuncture, acupuncture-like transcutaneous electrical nerve stimulation, low-level laser therapy and herbal medicine. A recent study evaluated the salivary parameters in 4 phases. Results of meta analysis suggests cholinergic agonists were the most effective to improve salivary flow, compared to placebo, although some aspects of the relevant effect size, duration of the benefit, and clinical meaningfulness remain unclear.

Conclusions: Pilocarpine, bethanechol and cevimeline should represent the first line of therapy in head and neck cancer survivors with radiotherapy-induced xerostomia and hyposalivation. The use of other treatment modalities cannot be supported on the basis of current evidence.

Legal entity responsible for the study: nil

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1100P The phase II study of HMB/Arg/Gln against oral mucositis induced by chemoradiotherapy for head and neck cancer patients

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Background: Opioid-based pain control and systemic oral care program are effective for the chemoradiotherapy (CRT)-induced severe oral mucositis (OM) in patients with head and neck cancers (HNC). This phase II trial assessed the clinical benefit of beta-Hydroxy-beta-Methylbutyrate, Arginine, and Glutamine (HMB/Arg/Gln) in the prevention of CRT-induced OM in patients with HNC.

Methods: Patients with HNC who were scheduled to receive definitive or postoperative cisplatin-based CRT were enrolled. HMB/Arg/Gln was administered orally or per percutaneous endoscopic gastrostomy from the first day of CRT up to completion of CRT. All patients received opioid-based pain control and oral care programs we previously published. The primary endpoint was the incidence of grade $\geq$3 OM (functional/symptomatic) according to the Common Terminology Criteria of Adverse Events version 3.0. QOL (EORTC QLQ-C30/PROMS) and intake of nutrition at baseline and 50Gy were also assessed.

Results: From February 2015 to June 2016, 35 patients with HNC were enrolled. Sixteen patients (45.7%) developed grade $\geq$3 OM (i.e., functional/symptomatic). The incidence of grade $\leq$1 OM (functional/symptomatic) was 51.5% at 2 weeks and 82.9% at 4 weeks after completion of RT. Clinical examination revealed that 10 patients (28.6%) developed grade $\geq$3 OM. The incidence of grade $\leq$1 OM (clinical exam) was 80.0% at 2 weeks and 100% at 4 weeks after completion of RT. Only 5.7% of patients had unplanned breaks in radiotherapy, and all patients completed treatment. Adverse events related to HMB/Arg/Gln were increase in blood urea nitrogen and diarrhea, but were easily managed.

Conclusions: Addition of HMB/Arg/Gln to opioid-based pain control and oral care programs was feasible but still insufficient in reducing the incidence of severe CRT-induced oral mucositis. However, the benefit of HMB/Arg/Gln should not be neglected in terms of findings of clinical examination and the recovery from severe oral mucositis.

Clinical trial identification: UMIN000016453

Legal entity responsible for the study: None

Funding: Public Interest Incorporated Foundation- Shizuoka Industrial Foundation-Pharma Valley Center

Disclosure: All authors have declared no conflicts of interest.

1101P Oral mucosa dose parameters predicting grade $\geq$3 acute toxicity in locally advanced nasopharyngeal carcinoma patients treated with concurrent intensity-modulated radiation therapy and chemotherapy

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Background: To determine whether volumes based on the contours of the mucosal surface can be used instead of the contours of the oral cavity to predict for grade $\geq$3 acute oral mucosa toxicity in patients with locally advanced nasopharyngeal carcinoma (LANPC) treated with concurrent intensity-modulated radiation therapy (IMRT) and chemotherapy.

Methods: A standardized method for the oral cavity (oral cavity contours, OCC) and a novel method for the mucosal surface (mucosal surface contours, MSC) were developed for the oral mucosa and prospectively applied to the radiation treatment plans of 92 patients treated with concurrent IMRT and chemotherapy for LANPC. Dose–volume histogram (DVH) data were extracted and analyzed against patient toxicity. Receiver operating characteristic analysis and logistic regression were carried out for both contouring methods.

Results: Grade $\geq$3 oral mucosa toxicity occurred in 20.7% (19/92) of patients in the study. A highly significant dose–volume relationship between oral mucosa irradiation and acute oral mucosa toxicity was supported by using both oral cavity and mucosal surface contouring techniques. In logistic regression, body weight loss was an independent factor related to grade $\geq$3 toxicity for OCC and MSC (p=0.017 and 0.005, respectively), and the independent factor of dosimetric parameters for OCC and MSC were V30Gy (p=0.003) and V50Gy (p=0.003), respectively. In the receiver operating characteristics curve, the areas under V30Gy of the OCC curves was 0.753 (p=0.001), and the areas under V50Gy of MSC curves was 0.714 (p=0.004); the cut-off value was 73.155% (sensitivity, 0.842; specificity, 0.671) and 14.32% (sensitivity, 0.842; specificity, 0.575), respectively.

Conclusions: DVH analysis of mucosal surface volumes accurately predicts grade $\geq$3 oral mucosa toxicity in patients with LANPC receiving concurrent IMRT and chemotherapy, but the MSC method is still no better than the OCC method in clinical application.

Clinical trial identification: NCT02945878

Legal entity responsible for the study: Yuanyuan Chen

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1102P Sinonasal non-glandular cancers relapsing after multimodal treatments

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Background: Multimodality treatment (MMT) is the current approach to advanced sinonasal cancers (SC). We lack salvage treatment standardization especially for pts already receiving MMT. No clinical factors able to predict outcome have been identified in this disease setting.

Methods: We retrospectively analyzed a series of pts with recurrent/metastatic (RM) SC after multimodal curative treatment, consisting in induction chemotherapy (iCT) followed by locoregional therapy. Overall survival (OS) was measured as the interval from relapse to death.

Results: Among 106 pts with SC treated with MMT at our Center from 1997 to 2016, 50 (M/F 31/19) relapsed. Median age was 53 yrs (16-73). Median follow-up was 26 months (m) (5-192). WHO 2005 histotypes were: 36% sinonasal undifferentiated carcinoma (SNUC), 34% squamous cell cancer (SCC), 30% carcinomas with neuroendocrine differentiation (CND). Median time to first relapse after curative treatment was 13.5 m. Median OS was 13 m from recurrence: 19 m in SCC, 16 m in SNUC and 6 m in CND ($p = .34$). Relapse occurred as distant metastasis in 40%, as nodal recurrence in 6% and at primary site in 54% of cases. First line salvage treatment was surgery in 38% (14 pts received surgery on T, 2 on N and 3 on M), CT in 30%, RT in 8%, best supportive care in the remaining pts. Median OS was 31 m in surgically treated pts and 4.8 m in those receiving CT ($p < .0001$). In pts with disease control (PR+SD) after iCT, median OS after recurrence was longer than in pts with PD (13.4 vs 1.5 m, $p = .07$). Median OS from relapse was 29.6 m in pts with CR after definitive treatment, 7.1 m in those with PR and 3.4 m in those with PD ($p = .002$). Pts with an objective response to palliative CT had a longer median OS than those with PD (20 vs 4 m, $p = .002$).

Conclusions: Prognosis of SC relapsing after MMT is dismal. With the caveat of a retrospective analysis and a case series that has been collected in a long time frame, we showed that feasibility of salvage surgery, objective response to prior definitive treatment and response to palliative CT are factors associated with better outcomes. Pts with relapsed or metastatic SC not amenable to salvage surgery should be considered for enrolment in clinical trials.

Legal entity responsible for the study: Fondazione IRCCS Istituto Nazionale Tumori Milano - Università degli Studi di Milano. Italy

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1103P Survival outcome and optimal treatment of intermediate-grade salivary gland carcinoma

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Background: Histological grade is the most important factor for defining treatment strategies and predicting prognosis for salivary gland carcinoma (SGC). Although several studies have addressed low- and high-grade SGCs, intermediate-grade SGC (IGSGC) has received minimal attention. Therefore, we examined factors affecting long-term recurrence and survival among IGSGC patients to define optimal treatment modalities and outcomes.

Methods: We reviewed the clinical and pathological data of 108 IGSGC patients who underwent definitive surgery with or without postoperative radiotherapy at our tertiary referral center between 1994 and 2014. We performed univariate and multivariate analyses of variables predictive of locoregional control (LRC), distant metastasis-free survival (DMFS), and overall survival (OS). We compared treatment outcomes by treatment strategies such as surgical extent, primary tumor, neck dissection, or postoperative radiotherapy.

Results: During a median 103 (range, 24−282)-month follow-up, local, regional, and distant recurrences were detected in 14 (13.0%), 3 (2.8%), and 21 (19.4%) patients, respectively. The 10-year LRC, DMFS, and OS rates were 83.1%, 76.0%, and 80.1%, respectively. Multivariate analyses identified a non-parotid primary site as an independent prognostic factor for LRC ($P = 0.018$), Adenoid cystic carcinoma and positive pN classification were significantly unfavorable prognostic factors for DMFS ($P = 0.025$ and $P = 0.030$, respectively); overall advanced stage was an independent prognostic factor for OS ($P = 0.020$). Surgical extent, elective neck dissection, and postoperative adjuvant radiotherapy did not significantly affect treatment outcomes.

Conclusions: Patients with early-stage IGSGC of parotid origin can achieve favorable treatment outcomes with conservative surgery alone.

Legal entity responsible for the study: no

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1104P Incidence and survival of secondary malignances (SM) in oropharingeal squamous cell carcinoma (OPSCC): A homogeneous single report institution

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Background: SM in HNSCC patients (pts) are common, due to the presence of risk factors (smoking habit or alcohol abuse). Aim of this report is to evaluate the incidence and characteristics of SM in a series of OPSCC.

Methods: We retrospectively reviewed clinical data of 266 pts with OPSCC seen at Modena University Hospital between 2006 and 2016. We recorded data from a web platform in which every pt has a personal form filled with clinical information. In particular, we analyzed the rate of SM and described clinical and survival data.

Results: SM was diagnosed in 37 pts (13,9%): 15 NSCLC (5% on all; 40,5% of SM); 7 HNSCC (18,9%), 8 GI (21,6%), 2 prostate (5,4%), 2 thyroid cancer (5,4%), 2 hematologic malignancy (5,4%) and 1 melanoma (2,7%). Clinical features at diagnosis for OPSCC: 30 (81%) male, 7 (19%) female; median age 68 years (range 37-90). Twenty-five pts (67,6%) were current/former smokers, 26 (70,3%) HPV-positive; stage at diagnosis was I-II in 5 (13,5%) and III-IV in 32 pts (86,5%). Eleven pts developed SM < 12 vs 26 ≥ 12 months (mo) after the diagnosis of OPSCC. Stage at diagnosis for SM was: for lung 10 (66, 6%) I-II vs 5 (33,4%) III-IV; for HNSCC 3 (42,8%) I-II vs 4 (57,2%) III-IV; for GI 2 (25%) I-II vs 6 (75%) III-IV. Treatments for SM: 18 surgery, 2 RT, 8 CT, 5 combined treatment; 4 pts did not need or not received therapy. Death occurred in 18 pts (48,6%): SM-related in 12 (66,6%), OPSCC-related in 3 (16,7%) and not cancer-related in 3 (16,7%). mOS from diagnosis of OPSCC vs SM were 68,5 and 21,3 mo, respectively. Pts with lung or HNSCC SM (mOS 6,7 mo) had worse OS than pts with other SM (mOS 20,7 mo), but not statistically significant. Pts with SM diagnosed ≥ 12 mo vs < 12 mo after OPSCC had a significantly better OS (mOS 81 vs 25,1 mo; $p < 0.001$).

Conclusions: In our retrospective series, we confirmed that secondary lung cancer was the most frequent SM; it was diagnosed at earlier stage, because these pts underwent a periodical follow-up for their previous OPSCC with a chest X-ray/CT. Smokers may benefit from a more intensive follow-up for a higher risk of smoking related SM (lung, HNSCC). Survival is more influenced by the occurrence of SM than by OPSCC. All these considerations should be applied to a larger series.

Legal entity responsible for the study: Modena University Hospital

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1105TiP Pembrolizumab plus chemoradiation (CRT) for the treatment of locally advanced head and neck squamous cell carcinoma (LA-HNSCC): Phase 3 KEYNOTE-412 trial

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Background: Despite significant advancements in oncologic treatment, the outcome for patients with advanced or recurrent HNSCC is poor. Identification of abscopal effects by use of radiotherapy (RT) in combination with immunotherapy in a patient with metastatic melanoma has prompted interest in the use of combination regimens. The objective of the KEYNOTE-412 trial (NCT03040999) is to assess efficacy and safety of pembrolizumab in combination with CRT as maintenance therapy for subjects with LA-HNSCC.

Trial design: KEYNOTE-412 is a phase 3, randomized, placebo-controlled, double-blind trial enrolling subjects with newly diagnosed, treatment-naive, oropharyngeal p16 positive (any T4 or any N3), oropharyngeal p16 negative (any T3-T4, or N2a-N3), or larynx/hypopharynx/oral cavity (any T3-T4, any N2a-N3) SCC. Approximately 780 subjects will be randomly assigned (1:1) to receive pembrolizumab plus cisplatin-based CRT or placebo plus cisplatin-based CRT. Subjects will be stratified by RT regimen, tumor site/p16 status, and disease stage. Treatment will include a priming dose of pembrolizumab 200 mg or placebo 1 week before initiation of CRT, followed by 7 weeks' CRT (cisplatin 100 mg/m^2 every 3 weeks [Q3W] [3 doses]; accelerated RT [70 Gy, 6 fractions/week] or standard RT [70 Gy, 5 fractions/week]) plus pembrolizumab 200 mg Q3W or placebo Q3W. Treatment with pembrolizumab 200 mg Q3W or placebo Q3W will continue up to 1 year (maximum 17 doses). Treatment will continue until disease progression, unacceptable toxicity, withdrawal of consent, or investigator decision to withdraw the patient. Response will be assessed by computed topography or magnetic resonance imaging 12 weeks after completion of CRT, every 4 months for a subsequent 2 years, and every 6 months thereafter up to year 5. Safety will be monitored throughout the study. The primary end point is event-free survival by blinded independent central review per RECIST v1.1. Secondary end points include overall survival, safety, and quality of life. Exploratory biomarker analyses will be conducted.

Clinical trial identification: NCT03040999, February 1, 2017

Legal entity responsible for the study: Merck & Co., Inc., Kenilworth, NJ, USA

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1106TiP Hope for salivary gland cancer (SGC): EORTC HNCG/UKCRN 1206 randomized phase II study to evaluate the efficacy and safety of Chemotherapy (CT) vs androgen deprivation therapy (ADT) in patients with recurrent and/or metastatic androgen receptor (AR) expressing SGC

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Background: SGCs are rare and heterogenous tumors (<1% of all malignancies in Europe). Among more than 20 histotypes, only salivary duct carcinoma (SDC) and adenocarcinoma NOS expresses AR. These variants are aggressive and associated with poor prognosis. Surgery is the main curative treatment but upon relapse, patients are left with very few options. There is an urgent need to understand their biology to enable progress in this rare disease. This study (NCT01969578) aims to evaluate the efficacy and safety of ADT (experimental arm) vs chemotherapy (standard arm) in patients with recurrent and/or metastatic, AR overexpressing SDC and adenocarcinoma, NOS

by demonstrating a 15% improvement in Progression Free Survival (PFS) rate at 6 months in favor of ADT.

Trial design: In this multicenter, randomized, phase II intergroup study a total of 76 treatment naïve patients (Cohort A) are planned to be randomized to receive ADT or platinum-based chemotherapy. Previously treated patients will be enrolled in a separate Cohort B to receive ADT. Patients from Cohort A randomized to chemotherapy can also enter Cohort B at disease progression. The primary endpoint is PFS for Cohort A and best overall response for Cohort B. Central testing of AR expression is based on staining intensity (0 = negative to 3 = strong) and percentage of positive nuclear stained cells (0 = ≤10% to 3 = ≥70%). AR overexpression requires a maximum score of 3 on both scales. Mechanisms of AR activation and resistance will be studied. This study is led by EORTC Head and Neck Cancer Group with UNICANCER/REFCOR, International Rare Cancer Initiative UK Salivary Gland Cancer Group and RARECARENet. It will run in 35 sites in 10 countries: Austria, Belgium, France, Germany, Greece, Hungary, Italy, Portugal, The Netherlands, and United Kingdom. Sites from the EURACAN European Reference Network are participating. Currently, 36 patients are registered; 20 have AR overexpression, of which 16 have been randomized in Cohort A. Identification of AR as a treatment target in SGC can be practice changing.

Clinical trial identification: EORTC 1206 HNCG http://clinicaltrials.gov/ct/show/NCT01969578

Legal entity responsible for the study: European Organization for Research and Treatment of Cancer

Funding: EORTC ICR RARECAREnet Fondazione IRCCS Istituto Nazionale dei Tumori

Disclosure: All authors have declared no conflicts of interest.

1107TiP Phase II trial of abiraterone acetate in patients with relapsed and/or metastatic, castration resistant AR expressing salivary glands carcinomas (SGCs)

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Background: Expression of androgen receptors (AR), is reported in more than 80% of salivary duct carcinomas (SDC) and in 50% of adenocarcinomas, NOS. Similary to prostate cancer (Pca), androgen deprivation therapy (ADT) has been employed with success in patients with metastatic AR-expressing SDC and adenocarcinoma, NOS in so much as an international randomized trial is ongoing to assess the efficacy of ADT over chemotherapy as first line treatment in this setting of patients (NCT01969578). Abiraterone acetate was approved in advanced, castration resistant Pca in 2011. We tested the activity of abiraterone in two patients with AR-positive castration resistant adenocarcinoma, NOS obtaining two partial responses (Locati LD, Cancer Biol Ther 2014).

Trial design: This is a phase II trial (NCT02867852) aimed at assessing the activity (CR+ PR) of abiraterone in castration resistant AR-positive SGCs. The drug will be considered effective and worth of further evaluation if the response rate will be at least 20%. The null hypothesis will be RR 5% versus the alternative RR20%. A 2-stage Simon design will be applied. Type I and type II error rates are set at the 10% and 20% levels. If at least 1/9 response will be observed in the first step, patients' enrolment will go on up to a final overall sample size of 24 subjects. If at least 3/24 responses will be recorded, the null hypothesis will be rejected in favor of the alternative and the drug considered promising and worthy of further investigation. Objective tumor response and time to progression will be measured according to RECIST criteria 1.1 and to PCWG2 recommendations for bone lesions. Twenty four patients with AR-expressing SGC, progressed on ADT, will be enrolled over two years. Four 250 mg tablets of abiraterone acetate will be administered daily to patients until progression of disease or intolerable toxicity. Disease control rate, incidence of adverse events, overall survival and progression free survival will be assessed as well. Tumor samples will be also collected for translational analyses (e.g. CYP17 expression; PI3K mutations). Blood and saliva samples will be collected as well.

Clinical trial identification: NCT02867852

Legal entity responsible for the study: Fondazione IRCCS Istituto Nazionale dei Tumori Milan, Italy

Funding: Fondazione IRCCS Istituto Nazionale dei Tumori

Disclosure: All authors have declared no conflicts of interest.

1108TiP Chemoradiotherapy versus radiotherapy in the treatment of salivary glands and nasal tumors: The GORTEC 2016-02 study

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Background: Carcinomas of sinuses and salivary glands are rare and heterogeneous in terms of anatomical sites and histology subtypes. For these reasons and because of the absence of prospective study results, their treatment is still largely extrapolated from data of frequent carcinomas of the upper digestive tract. Treatment is based on surgery and radiotherapy (proof level grade C). Despite the advances, the 5-year overall survival does not exceed 65%, mainly due to locoregional recurrence. In this context, chemotherapy administered concomitantly with radiotherapy could increase the efficacy of locoregional treatment by radiosensitization, regardless of the histology.

Trial design: The GORTEC launched a multicenter, phase III randomized, open-label, study evaluating in case of high-risk of locoregional relapse, the impact of the addition after surgery of cisplatin 100 mg/m^2 (every 3 weeks; 3 cycles) to radiotherapy. The population is defined as patients with radioresistant histologies (e.g. cystic adenoids carcinomas) or patients with unfavorable histoprognostic critera (e.g. incomplete resection, T4 tumor, malignant lymph node(s) with capsular rupture, presence of emboli, . . .). The primary endpoint is the progression free survival. Secondary outcomes are: overall survival, quality of life, time to progression (locoregional and distant) and toxicities. Two hundred and sixty patients will be enrolled in 5 years. Eligible patients are adults, with a performance status ≤ 2 and an adequate hematological and renal function for cisplatin treatment. Recruitment is ongoing in France. The study comprises a quality insurance program in radiotherapy and surgery. Coordinating investigators are Drs Ferrand and Thariat.

Clinical trial identification: NCT02998385.

Legal entity responsible for the study: GORTEC (Groupe Oncologie Radiothérapie Tête et Cou)

Funding: GORTEC

Disclosure: All authors have declared no conflicts of interest.

1109TiP MEDINDUCTION: Phase I trial evaluating the safety of durvalumab in combination with Docetaxel, Cisplatin and 5-FU (DCF) in induction for locally advanced squamous cell carcinoma of the head and neck (SCCHN)

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Background: SCCHN represents the sixth most common malignancy with 650 000 new cases and 350 000 SCCHN-related deaths reported annually worldwide. A majority of patients present with stage III or IV M0 disease, with a 5 year overall survival from 30% to 50%. Results of recent randomized trials evaluating induction chemotherapy by DCF are conflicting, and benefit on overall survival is uncertain. It is needed to improve efficacy of induction chemotherapy without increase toxicities. Tumours can actively evade destruction by the immune system by exploiting inhibitory checkpoint pathways that suppress antitumour T-cell responses. Antibody therapy to block immune checkpoints activated by the programmed cell death ligand-1 (PD-L1) has shown survival benefit in recurrent or metastatic SCCHN. Durvalumab is a selective, high affinity, engineered human IgG1 mAb that blocks PD-L1 binding to PD-1 and CD80. Durvalumab has shown encouraging antitumour activity in SCCHN with a manageable safety profile. The aim of this open-label, multi-center, Phase 1-b study is to characterize the safety profile of the combination of DCF with durvalumab.

Trial design: Patients aged ≥ 18 yr with histologically confirmed SCC of the oral cavity, oropharynx, larynx or hypopharynx, previously untreated, with indication of induction chemotherapy will be eligible. The primary objective is to determine the recommended Phase 2 dose (RP2D). The secondary objectives are to document any antitumor activity (PFS, ORR, RECISTv1.1 criteria), to estimate the pharmacokinetic parameters of durvalumab, to explore the relationships between immune capacity, specificity, activation state and clinical outcome. The study will be conducted in 2 parts: a dose-deescalation part to determine the RP2D (6 pts), and an expansion part (30 pts). The durvalumab will be administered every 3 weeks for 3 injections at week 1, 4, 7. The durvalumab first dose level is 1120 mg and the dose level -1 is 750 mg Q3W. The chemotherapy will be administered every 3 weeks at week 1, 4, 7 at the following doses: Docetaxel 75mg/m^2 on D2, Cisplatin 75mg/m^2 on D2, 5 Fluorouracil 750mg/m^2/day from D2 to D6.

Clinical trial identification: NCT 02997332 Eudract number 2015-004146-25

Legal entity responsible for the study: Gustave Roussy

Funding: INCA and ARC Aknowledgement to Astra Zeneca for providing the drug

Disclosure: C. Even: Advisory board: AstraZeneca, Bristol-Myers Squibb, Innate Pharma, Merck Serrono, MSD. C. Le Tourneau: Consulting fees: AstraZeneca. J. Fayette: Honoraria: Bristol-Myers Squibb, AstraZeneca. All other authors have declared no conflicts of interest.

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

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HEALTH ECONOMICS

1111PD Economic burden of cancer patients and the job assistance from the society

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Background: Cancer patients who face the financial difficulties and are obliged to retire for the treatment are increasing in number. It is urgently important that they keep working to receive the optimal treatment. We investigate the actual situation of the patients who retired for treatment and examine the feasible measures including the desirable balance of work and treatment.

Methods: The cancer patients and the attending doctors were surveyed in 40 cancer centers, university hospitals and regional hospitals in Japan.

Results: The number of replies from patients was 3.204. The ratio of patients who were at work before treatment was 50.7%. The ratio of employees was 89.7%. Of these, 31.8% of patients quitted their work for treatment. It was as the highest as 38.7% in lung cancer, and as the lowest as 27.1% in breast cancer. In case of retirees, the ratios of stage I, II, III and IV were 20.6%, 17.9%, 13.9% and 43.7% respectively. The ratio of stage IV was 26.8% in the whole patients, and therefore the retirees tend to be higher in stage. The annual out-of-pocket expense, including direct and indirect expense in the retirees was an average of 6,940 EUR. This was slightly smaller than that of the whole patients. The ratios of patients who felt heavy about the economic burden were 73.7% in retirees and 61.9% in the whole patients. 7.0% of retirees and 5.3% of the whole patients had to change or abandon the most suitable treatment due to the economic reasons. 58.5% of retirees answered that the income was decreased during the cancer treatment and this was significantly higher than that of the whole patients. The percentage of retirees whose tax-included annual income was less than 24,200 EUR was 48. 6%. This was 39.2% in the whole patients. 46.7% of retired employees had no choice but to quite the work, while 42.7% answered that they wanted to continue their work.

Conclusions: One of three patients with cancer is in a working generation, and it is important for patients to balance the treatment with the work. It became clear in the survey that one third of the patient who was working was obliged to retirement. In Japan, the Cancer Control Act was revised in December, 2016 and it became the efforts duty of the company to continue the employment of cancer patients.

Legal entity responsible for the study: Nobuo Koinuma

Funding: Ministry of Health, Labor and Welfare

Disclosure: All authors have declared no conflicts of interest.

1113PD Using the ASCO's quality oncology practice initiative (QOPI) metrics and standards to improve value, meaningful use of resources and reduce waste

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Background: The Institute of Oncology (IOV) is using the ASCO's QOPI since 2013 in Brazil. QOPI is a retrospective analysis by data abstraction submited to a database pulling over 180 quality measures based on care guidelines and expert consensus. Data collection are twice a year and provides reports based on practice wide data sample comparing overall quality score for the practice and for the participants aggregate.

Methods: IOV participates in rounds at least once a year. At each round current performance is reviewed and select gaps are translated into improvement projects that focus on meaningful use of resources, safety, accountability of care, and value. Meaningful use of PET-CT; lab tests; and G-CSF are samples of specific projects the past. IOV's Patient Navigation System (PNS) was adapted to track QOPI standards/measures that are monitored by clinical navigators as checkpoints in real time transitions of care and handovers. Potentially hazardous checkpoints are actively chased using a daily signaling process.

Results: Between Feb/2016 and Mar/2017, the PNS checked 9,372 patient iteractions (surgery, exams, outside appointments, optimal sequencing of care); 138 (1.5%) potentially hazardous events were identifiifed and managed in advance: missing "readiness to care data" and lab tests (36%); delayed radiation or chemo (38%); delayed surgery (7%); and missing echocardiogram for patients using cardiotoxic drugs (6%). The Pain Management Navigation System was created to meet another set of QOPI measures that also translated into 17% reduction of emergency room admissions for 141 patients involved. A dedicated flow was created to meet oral chemo standards, and patient satisfaction improved from 67% to 93% by reducing door-to-door time from 40 to 12 minutes, including check in, interview, drug refill and reconciliation.

Conclusions: One of the big challenges of healthcare is how to introduce changes that translates into real improvements. The use of evidence-based measures and standards to evaluate quality of care provides a clear and straight path to deliver higher value; meaningful use of resources; focus and alignment for improvements initiatives where it matters most: patient care and outcomes.

Legal entity responsible for the study: Instituto de Oncologia do Vale

Funding: None

Disclosure: C.F. Pinto: Board Member at Institute of Oncology. All other authors have declared no conflicts of interest.

1114P All.Can initiative: improving efficiency in cancer care

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Background: In industrialised countries, about 20% of healthcare spending is currently wasted on ineffective interventions. With growing cancer prevalence and the increasing complexity of care, efficiency must improve – defined as delivering better outcomes to patients for the resources available.

Methods: The All.Can initiative was set up as a multi-stakeholder platform to engage policymakers on the need to remove obsolescence and focus resources on what matters most to patients across the cancer care continuum. Members of the group include patient organisations, policymakers, healthcare professionals, research and industry representatives from across Europe and Canada. All.Can has a continued programme of research and policy engagement to achieve its aims.

Results: The group issued the following policy recommendations: focus care on what matters most to patients; invest in data to evaluate and monitor whether care is delivering optimal outcomes; instil accountability mechanisms across the cancer care pathway, creating a cycle of continuous improvement; and build political to drive meaningful change to systematise good practice. As a starting point however, we need clear definitions of waste and inefficiency from the patient perspective. All.Can will conduct a comprehensive qualitative survey of cancer patients to create a patient-relevant conceptual framework for waste and inefficiency. The survey will also be extended to oncology specialists. Findings will help determine where greatest opportunities lie to improve efficiency in cancer care, and serve as a basis for concrete policy proposals that may make the greatest difference to cancer patients.

Conclusions: Improving efficiency across the entire cancer care pathway is a complex and pressing challenge that will require close collaboration between all stakeholders. The All.Can initiative is a promising way forward.

Legal entity responsible for the study: The Health Policy Partnership Ltd

Funding: Bristol-Myers Squibb, Amgen and MSD

Disclosure: A. Roediger: Employment with MSD. T. Rosvall-Puplett: Employment with Bristol-Myers Squibb. K. Steinmann: Employment with Amgen. S. Wait: Received consultancy fees from Amgen, MSD and Bristol-Myers Squibb (the funders of All.Can) through organisation, the Health Policy Partnership, for providing secretariat to All.Can. All other authors have declared no conflicts of interest.

1115P Cost-effectiveness of nivolumab+ipilimumab in first-line treatment of advanced melanoma: Analysis using 28-month overall survival from CheckMate 067

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Background: The objective of this study is to evaluate the cost-effectiveness of nivolumab+ipilimumab (NIVO+IPI) versus existing treatments in first-line treatment of patients with advanced melanoma from a US payer perspective using recently reported 28-month survival data from the CheckMate 067 phase III trial.

Methods: This three-state partitioned survival model was developed from projections of overall survival (OS) and progression-free survival (PFS) based on a network meta-analysis that considers time-varying hazard ratios to estimate accrued quality adjusted survival, total drug acquisition, follow-up, and toxicity costs over a lifetime time horizon (30 years). Competing treatments included NIVO, IPI, pembrolizumab (PEM), dabrafenib+trametinib (DAB+TRA), DAB, vemurafenib+cobimetinib (VEM+COB), VEM, and dacarbazine (DTIC). Costs and adverse event frequencies were obtained from expert input, publically available sources, and literature. Utility weights were estimated from the CheckMate 067 trial. Incremental analysis is summarized as incremental cost-utility ratios (ICURs) for NIVO+IPI. A 3.5% discount rate is applied to costs ($US 2016) and utilities.

Results: NIVO+IPI is projected to have the greatest accrued survival among the competing treatments with 6.015 LY and 4.979 QALY and also the highest costs ($291,096 including treatment acquisition, follow-up, management of adverse events, and post-progression costs) over the 30-year time horizon. Pairwise ICURs for NIVO+IPI vs. other treatments ranged from $34,774 per QALY (vs. DAB+TRA) to $92,647 per QALY (vs. NIVO). In extended dominance analysis, DTIC, NIVO, and NIVO+IPI form the cost-effectiveness frontier, showing that these are the most cost-effective options at different willingness to pay thresholds. Probabilistic sensitivity analysis generated results consistent with the base case for NIVO+IPI.

Conclusions: The large survival gains of NIVO+IPI make it a cost-effective option for first-line treatment of advanced melanoma when compared to other immune-oncologic therapies, targeted agents, and chemotherapy.

Clinical trial identification: Cost study based on the 067 trial NCT01844505 protocol number is CA209-067 (CheckMate 067)

Legal entity responsible for the study: Bristol-Myers Squibb

Funding: Bristol-Myers Squibb

Disclosure: J. Sabater, K. Gupte-Singh, S. Kotapati, S. Rao: Employed by Bristol-Myers Squibb and owns stock in Bristol-Myers Squibb. T. Baker: ICON is contracted to undertake the nivolumab analysis for Bristol-Myers Squibb and ICON pays me as a consultant to the project. V. Paly: Outside of support received from Bristol-Myers Squibb in preparation of the core model and market specific adaptations. A. Briggs: ICON is contracted to undertake the nivolumab analysis for Bristol-Myers Squibb and ICON pays me as a consultant to the project. All other authors have declared no conflicts of interest.

1116P Palbociclib in advanced breast cancer: A cost-utility analysis

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Background: The addition of *palbociclib* to *letrozole* improves progression free survival (PFS) and response rates compared to *letrozole* alone in the 1st line treatment of hormone receptor positive advanced breast cancer (ABC). This study assesses the cost-utility of *palbociclib* from the Canadian healthcare payer perspective.

Methods: To evaluate the cost-utility of *palbociclib*, a probabilistic discrete event simulation model was developed. The model was parameterized with data from the phase 2 and 3 PALOMA 1 and 2 trials and other sources. The incremental cost per quality-adjusted life-month (QALM) gained for *palbociclib* was calculated. A time horizon of 15 years was used in the base case with costs and effectiveness discounted 5% annually. The time to progression and death were derived from Weibull and exponential distributions, respectively. Expected costs were based on Ontario fees and other sources. Probabilistic sensitivity analyses were conducted to account for parameter uncertainty.

Results: Compared to *letrozole* alone, the addition of *palbociclib* provided an additional 14.7 QALM at an incremental cost of $161,508. The resulting incremental cost-effectiveness ratio was $10,999/QALM gained. Assuming a willingness to pay (WTP) of $4167 per QALM, the addition of *palbociclib* was not cost-effective and the probability of *palbociclib* to be cost-effective was 0%. Cost-effectiveness acceptability curves derived from a probabilistic sensitivity analysis showed that at a WTP of $11,667/QALM gained, the probability of *palbociclib* to be cost-effective was 50%.

Conclusions: Compared with *letrozole* alone, the addition of *palbociclib* is unlikely to be cost-effective for the treatment of ABC from a Canadian healthcare perspective with its current price. While ABC patients derive a meaningful clinical benefit from *palbociclib*, considerations should be given to increase the WTP threshold and reduce the drug pricing, to render this strategy more affordable. Model validation and calibration are needed to confirm those results.

Legal entity responsible for the study: Jacques Raphael

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1117P Real-world survival outcomes in patients with advanced urothelial cancer in Germany

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Background: Contemporary data from the advanced urothelial cancer (UC) setting are scarce. Here, we describe treatment (tx) patterns and outcomes among > 350 patients (pts) in Germany.

Methods: Data were extracted from pt medical records from office-based urologists and urology clinics in Germany. Adult pts (age ≥ 18 y) diagnosed with T4b, N2-3 and/or M1 UC and received first-line (1L) or second-line (2L) palliative chemotherapy from 2009 to 2016 were included. The index date was the start date of first systemic therapy. We described tx patterns and clinical characteristics; Kaplan-Meier method assessed overall survival (OS). Cox regression adjusted for age, Eastern Cooperative Oncology Group performance status (ECOG PS) and liver metastases, stratified by hospital/office, compared tx.

Results: Among 368 included pts, 356 and 107 received 1L and 2L tx, respectively. At the start of 1L therapy, mean age was 68 y, 73% of pts were male, 74% were current/ex-smokers and 63% had metastatic disease. In 1L, 75% of pts received dual-combination tx, most commonly gemcitabine + cisplatin (GemCis; 83%). In 2L, 74% received single-agent tx, most commonly vinflunine (66%). In 1L, 12-month OS was 60%, slightly higher with GemCis (65%) than with other tx (52%). No difference in OS by sex or smoking status was noted. Pts with and without renal impairment (creatinine clearance </≥ 60 mL/min) had a 12-month OS of 47% and 70%, respectively. 12-month OS among pts with ECOG PS 0-1 was 62% vs 54% among pts with ECOG ≥ 2. There was no OS difference between vinflunine and other 2L tx (Table) (hazard ratio, 1.11 [95% CI: 0.65, 1.90]). Median PFS was 6.8 months in 1L pts and 3.3 months in 2L pts.

Table: 1117P Milestone Overall Survival, %

	1L n = 356	2L n = 107[a]
Overall		
12 mo	60%	37%
24 mo	37%	17%
36 mo	21%	5%
GemCis[b] 1L vs other 1L		
12 mo	65% vs 52%	—
24 mo	40% vs 34%	—
36 mo	20% vs 21%	—
Vinflunine[b] 2L vs other 2L		
12 mo	—	38% vs 37%
24 mo	—	20% vs 16%
36 mo	—	9% vs NA[c]

[a]A total of 368 pts were included; shown here are 356 pts who initiated 1L tx and 107 pts who initiated 2L tx during the study (2009-2016). 88.8% (n = 95) of the 107 pts are a subset of the 356 pts who initiated both 1L and 2L during the study.
[b]Most common tx per line of therapy.
[c]Estimate could not be calculated due to insufficient follow-up time

Conclusions: Outcomes in advanced UC tx in pts in this large real-world data study are comparable with clinical trials. Despite frequent use of cisplatin-based 1L tx and vinflunine 2L tx, per recent guidelines, outcomes are generally still poor.

Legal entity responsible for the study: F. Hoffman-La Roche Ltd.

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Disclosure: G. Niegisch: Research funding: 4SC AG Lecturer: Pfizer Pharma GmbH, Pierre Fabre Pharma GmbH, Roche Pharma AG Consulting or Advisory Role: Bristol-Myers Squibb, Roche Parma AG, IMS Health AG, medac GmbH Travel, Accommodations, Expense: Pfizer Pharma GmbH, Roche Pharma AG, Bristol-Myers Squibb. S-W. Lin: Receive salary and stocks from Genentech/Roche. J. Pavlova: Employee: Roche. A. Gondos, A. Rudolph, G. Haas: Employed by QuintilesIMS during the study. M.W. Kramer: Received honories for advisory board memberships and presentations from Roche, Pierre Fabre, Bristol-Myers Squibb, Novartis, Bayer, Astellas, Sanofi, Ipsen and Eisai. All other authors have declared no conflicts of interest.

1118P Health related quality of life and utility weights of medical oncology inpatients

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Background: Health related quality of life (HRQoL) data and utilities derived from preference-based scales are needed for pharmacoeconomic studies. However, available data for hospitalized Medical Oncology patients are scarce or restricted to specific neoplasms. The aim of this work was to obtain health state utilities (HSU) from a heterogeneous population of cancer inpatients admitted to a Medical Oncology department.

Methods: Between Dec-15 and March-16, we prospectively collected HRQoL data from consecutive patients admitted to a Medical Oncology ward using EuroQoL 5-domains 5-levels instrument (EQ-5D-5L) and EQ-5D-5L visual analogic scale (VAS). Utility weights were assigned according to Spain social tariff using EuroQol crosswalk value sets. Non-parametric tests (Mann Whitney U, Kruskal-Wallis) were used to evaluate differences of HSU between groups.

Results: 215 patients were included; median age: 62 (16-88); ECOG: 1 (45%), 2 (43%), 3-4 (12%); site: lung (27%), breast (15%), colorectal (15%), urogenital (15%); stage: I-II (11%), III (15%), IV (74%); active anticancer treatment: 87%; death during admission: 17 (8%). Mean (SD) EQ-5D-5L HSU for all patients was 0.52 (0.41); VAS: 52 (2). Mean (SD) values for EQ-5D-5L domains: mobility, 2.21 (1.24); self-care, 2.23 (1.49); usual activities, 2.89 (1.41); pain/discomfort, 1.94 (1.29); anxiety/depression: 2.12 (0.94). Differences between groups are shown in Table.

Conclusions: Average utility (EQ-5D-5L) for Medical Oncology inpatients is 0.52; lowest scores in this population were obtained for pain/discomfort and anxiety/depression domains. Significant differences were observed between different ECOG levels, tumor stages, admission causes and type of treatment.

Legal entity responsible for the study: Francisco Ayala de la Peña

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1119P A trial-based EUROQOL EQ-5D health utility analysis in patients with classical Hodgkin's lymphoma

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Background: Pembrolizumab has shown a high response in patients classic Hodgkin lymphoma (cHL) patients who have experienced disease progression after brentuximab vedotin in KEYNOTE (KN)-087 and the results have been presented. This study aimed to evaluate the health-related quality of life (HRQoL) of the trial patients in KN087.

Methods: KN-087 is an ongoing single-arm multi-center, non-randomized Phase II trial evaluating pembrolizumab 200mg Q3W IV in patients with relapsed or refractory cHL. In KN-087, HRQoL data were collected at baseline and every drug administration over the 18 months of follow-up. HRQoL was assessed using both the EQ-5D and EORTC QLQ-C30 instruments. The generic health statuses assessed from both instruments were converted to population-based utility values using published algorithms. More specifically, US-based scoring was applied to US patients, UK-based scoring for UK patients and EU-based scoring for all other patients. HRQoL was reported by status of respond and disease progression. Response was defined based upon IWG criteria. Furthermore, stratified analyses were conducted to examine the health disabilities of the patients who experienced grade 3+ adverse events (AEs), and by ECOG performance and the number of prior therapies.

Results: Among 210 trial patients, HRQoL data were collected for 205 patients at baseline and the mean health utility score was 0.759 (95% CI 0.730-0.788). Mean health utility score among responders and non-responders was 0.826 (95% CI 0.811-0.842) and 0.760 (95% CI 0.718-0.801), respectively. The difference is considered clinically significant. Mean utility decreased from 0.820 (95% CI 0.807-0.833) for time spent prior to progression to 0.806 (95% CI 0.780-0.832) post disease progression. Progression-free patients who experienced grade 3+ AEs (N = 17) had a mean health utility of 0.736 (95% CI 0.662-0.811), compared with 0.825 (95% CI 0.811-0.838) among those did not.

Conclusions: The results showed a substantial HRQoL impact of R/R cHL. Treatment response was associated with significant clinically meaningful improvement in HRQoL. The utility estimates from the study are important for economic evaluations of treatments in R/R cHL patients.

Clinical trial identification: NCT02453594

Legal entity responsible for the study: Merck

Funding: Merck

Disclosure: E. Wu, J. Liao, A. Balakumaran: Employee of Merck & Co Inc.

1120P Real world comparison of common patient reported symptoms with health utility scores in cancer outpatients

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Background: Health utility scores (HUS), a form of health-related quality of life (HRQoL) assessments useful in economic analyses, such as the EuroQol (EQ-5D) were originally standardized to health state preferences in healthy individuals. To demonstrate clinical appropriateness in cancer patients, we assessed the association of common cancer symptoms with EQ-5D HUS.

Methods: Adult cancer outpatients were surveyed cross-sectionally using the Edmonton Symptom Assessment System (ESAS), the EQ-5D-3L, and clinico-demographic variables. ESAS rated symptoms from 0-10. HUS were derived from the EQ-5D-3L (Canadian conversion). ESAS symptoms were correlated with HUS using Spearman correlation coefficients (R). Multivariable regression analyses identified independent variables associated with HUS.

Results: Of 764 patients across multiple cancers, 27% were palliative at assessment. There were significant correlations between each ESAS symptom score and HUS ($p < 0.0001$ for each comparison; Spearman coefficients: 0.20 to 0.42); the highest were for pain ($R = 0.42$), fatigue ($R = 0.39$), and depression ($R = 0.35$). In multivariable analyses, pain and depression symptom scores remained highly associated with HUS ($p < 0.0001$ each), while fatigue was of borderline significance ($p = 0.059$). Despite correlations, prediction of HUS by global ESAS scores was poor, with the highest prediction ability at 0.25. Because ESAS and EQ5D shared common symptom questions (pain, depression/anxiety), we evaluated if we could map and replace these EQ5D questions with ESAS. Spearman correlation of pain symptoms by EQ5D and ESAS was 0.95, while for depression/anxiety, 0.90. Replacing both questions yielded a correlation of 0.83.

Conclusions: HUS is associated with many cancer symptoms, including pain, fatigue, nausea, depression, anxiety, drowsiness, loss of appetite, and shortness of breath. EQ-5D-3L derived HUS have clinical utility. On exploratory analysis, we cannot replace

Table: 1118P HRQoL values (mean) and differences according to clinical characteristics

Clinical characteristics	Patients (n = 215)	EQ-5D-5L utility	p	EQ-5D-5L VAS	p
ECOG 1 2 3-4	96 92 27	0.77 0.41 0.04	<0.001	63 45 34	<0.001
Stage I-II III IV	23 32 154	0.79 0.68 0.46	<0.001	64 56 49	0.001
Active treatment Yes No	187 28	0.56 0.26	0.001	53 45	0.04
Cause of admission Febrile neutropenia Symptom worsening Others	18 53 129	0.81 0.16 0.61	<0.001	65 38 55	<0.001

accurately the EQ5D with ESAS, although we can replace two symptom questions within EQ5D with ESAS with high correlation.

Legal entity responsible for the study: Princess Margaret Cancer Centre, UHN, Toronto, Canada

Funding: Cancer Care Ontario

Disclosure: All authors have declared no conflicts of interest.

1121P Costs of dacomitinib versus placebo in pretreated unselected patients (pts) with advanced NSCLC: CCTG BR.26

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Background: Dacomitinib, a potent irreversible pan-HER kinase inhibitor, has activity in EGFR mutant (mt) lung cancer. BR.26, completed in 2013, compared dacomitinib versus placebo in unselected pts who had received both chemotherapy (1 or 2 lines) and a first-generation EGFR TKI for advanced NSCLC. Dacomitinib pts had significantly improved tumour response rate, PFS, and time to symptom deterioration but not improved survival (OS). A trend towards improved OS was seen in pts with KRAS wildtype (wt) tumours (KRAS unknown in 42%). A prospective economic evaluation was planned for Canadian and Australian pts.

Methods: Resource utilization and utility scores (EQ5D-3L) were collected prospectively in 385 trial participants from Canada and Australia. Direct medical costs were applied to resources in 2015 Canadian dollars (CAD) from the Canadian public health care payer perspective. Dacomitinib is not approved for marketing, thus we used a range of plausible drug costs (0-$120/mg). Restricted mean survival time, utility, and costs per arm were calculated, and explored in KRAS wt and EGFR mt subgroups.

Results: Incremental outcomes and costs by treatment arm are shown below. Mean utility scores were similar, although higher in dacomitinib-treated pts with KRAS wt or EGFR mt tumours (range u = 0.41- 0.55). Mean quality-adjusted survival was approximately 1 month longer with dacomitinib in both KRAS wt and EGFR mt subgroups. Direct medical costs excluding dacomitinib were similar between arms. Exploratory estimates of cost-utility ranged from $26,369-$184,701/QALY in KRAS wt, and $2,243-$133,953/QALY in pretreated EGFR mt pts.

Conclusions: Dacomitinib in previously treated, unselected NSCLC may yield minor gains in quality-adjusted survival without increasing other costs of care. Analyses of mutation status by ctDNA are ongoing.

Clinical trial identification: 2009-016509-41

Legal entity responsible for the study: Canadian Clinical Trials Group (CCTG)

Funding: Pfizer

Disclosure: P. Bradbury: Honorarium from Pfizer and Merck. P. Ellis: In the past two years, received honoraria for talks from Boehringer Ingelheim and Novartis. G. Liu: Honoraria from AstraZeneca, Pfizer, Novartis and Takeda. R. Sangha: Honoraria from: Pfizer, Boehringer Ingelheim, AstraZeneca, Roche, Eli-Lilly, Bristol-Myers Squibb and Merck. M. Boyer: I've received Honoraria (paid to my institution) from Pfizer, Boehringer Ingelheim and Astra Zeneca. G. Goss: Honoraria from Pfizer, AstraZeneca, Boehringer Ingelheim, Lilly, Bristol-Myers Squibb, and Celgene. L. Seymour: Pfizer provided funding for the BR.26 trial. N.B. Leighl: Research funding (institution) - Novartis Unrelated CME (not speaker's bureau) - travel/honoraria - AstraZeneca, Merck Sharpe Dohme, Pfizer, Bristol-Myers Squibb. All other authors have declared no conflicts of interest.

Table: 1121P

Incremental mean outcome with dacomitinib over placebo	All patients (n = 385)	*KRAS* wild type (*KRAS* known n = 165)	*EGFR* mutant (*EGFR* known n = 80)
Survival (ΔE, years)	0.0014	0.104	0.129
Quality-adjusted survival (ΔE, QALY)	0.011	0.069	0.088
Cost (ΔC, 2015 CAD) Set drug price at: $0/mg $40/mg $80/mg $120/mg	$524 $3,944 $7,363 $10,783	$1,829 $5,489 $9,149 $12,809	$199 $4,083 $7,968 $11,853

1122P Feasibility of routine collection of health state utilities using EQ-5D in a breast cancer outpatient clinic

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Background: Routine collection of health state utilities in the clinical setting may produce data more representative of the real-world population for use in cost-utility models and guide decision making. We are currently carrying out a cross-sectional study to assess the feasibility of routine administration of EQ-5D to breast cancer patients in a multidisciplinary oncology clinic, in an academic cancer centre in Ontario, Canada.

Methods: English literate women undergoing treatment or on follow-up for their breast cancer (stage I to IV), are being recruited during their scheduled visit to the cancer centre, preferably after completing the implemented routine symptom screening using the Edmonton Symptom Assessment System (ESAS). Consenting patients complete EQ-5D-5L in tablets, followed by a socio-demographic questionnaire and feedback questions pertaining to study conduct. Answers are stored in a research database and linked to diagnostic and treatment data. Feasibility will be assessed primarily by the proportion of patients who fully complete EQ-5D and by their willingness to complete the instrument at each clinic visit.

Results: To date, 474 women were approached; 262 (55%) were eligible and consented to participate (target enrolment: 341). Median age of participants was 56 years (range:28-90); 24% had metastatic disease. All participants were English literate, but 59% were born outside Canada and speak primarily other languages at home. Ninety-eight percent of recruited patients completed EQ-5D, compared with 84% who completed ESAS on the same day (63% completed ESAS voluntarily prior to enrolment; 21% agreed on completing ESAS for study purposes only). Median time for EQ-5D completion was 84 seconds. Most patients (82%) had no problems using the tablet. Willingness to continue to complete EQ-5D at each clinic visit was not affected by disease status (stage I to III versus stage IV) and 74% would "definitely"/"very likely" continue to answer EQ-5D regularly at each clinic visit.

Conclusions: These preliminary results indicate that routine collection of EQ-5D in clinical practice might be feasible, although the completion rate might be overestimated by the cross-sectional design of the study.

Legal entity responsible for the study: Sofia Torres

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1123P The cost of expensive breast cancer drugs

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Background: Increasing healthcare costs are a major challenge in medical oncology, since the total costs of oncology can account for up to 30% of the total hospital expenditures. As many novel (expensive) cancer treatments are being developed, it is important to be transparent about drug prices from an early research stage on. To assess the potential financial impact of pipeline drugs, their expected future prices can be deducted from prices of currently used drugs. As an overview of the standard prices of expensive breast cancer treatments in European countries is lacking, this review aimed to synthesize all evidence on costs of approved, expensive breast cancer drugs in the Netherlands.

Methods: A literature review was performed to create an overview of all approved, expensive drugs in the Netherlands. Standard drug costs were retrieved via the Dutch administrative health authority (ZINL). Drugs were considered expensive if the standard price of the drug was more than €10 per unit or if the cost of a treatment with that particular drug exceeded €1000 on average per patient.

Results: In the Netherlands 25 breast cancer drugs are approved with a standard price of more than €10 per unit. After excluding drugs with expected treatment costs less than €1000, 19 drugs were included in the analysis. The standard drug price is €7,943 on average (range €63 - €45,452), and the average number of cycles per patient is 10.5 (range 4 - 25.3 cycles). This results in average treatment costs per patient of expensive drugs of €17,968 (range €1,103 - €87,123). Four drugs that initially ranked low based on standard drug unit prices (rank 10-19), rank substantially higher (rank 1-10) when ranking total treatment costs.

Conclusions: Ranking standard drug prices per unit may not be very informative. It would be valuable to rank drug treatment costs, based on treatment length and dosage estimates. However, in the Netherlands the expected treatment length for a particular drug is not standardly reported in official approval reports. Furthermore, actual prices of expensive drugs may differ from standard drug prices, by which treatment costs might be deviant. Extending standardization of reporting and calculation of drug treatment costs would be valuable and particularly relevant when extending this type of cost calculations to other countries.

Legal entity responsible for the study: University of Twente - Health Technology and Services Research

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1125P The cost-effectiveness of EndoPredict to inform adjuvant chemotherapy decisions in early breast cancer

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Background: Chemotherapy alongside endocrine treatment in ER +ve breast cancer patients post resection of a primary tumour has been estimated to reduce mortality rates by up to 30%. However, the high cost of the therapies, heterogeneous nature of the disease and adverse event profile implies that not all patients should receive the treatment. Many existing prognostic tools such as the NPI, PREDICT, and Adjuvant! Online may not definitively estimate the risk profile of patients, resulting in an *indeterminate* risk classification. In such cases gene expression profiling tests such as EndoPredict can aid the treatment decision. It is important to examine if the test represents a cost-effective use of limited NHS resources in such intermediate risk patients.

Methods: This small (n = 151) multi-centre, two-stage study evaluated the cost-effectiveness of EndoPredict in patients with no clear treatment based on current prognostic criteria. The primary analysis examined whether EndoPredict test results increased or decreased the use and intensity of chemotherapy and the associated direct cost implications. Secondly, a mathematical model was constructed to determine how the change in treatment decisions impacted the long term health of the population, and the future cost implications to the NHS.

Results: A cost increase per patient treated with chemotherapy was identified when EndoPredict test results were available (£149), alongside no significant change in the total number being prescribed chemotherapy. However, chemotherapy was offered to a very different patient population, with 36.9% of patients having a change in treatment decision. The long term analysis found the use of EndoPredict to be associated with greater total costs but a potential increase in population health, resulting in an incremental cost-effectiveness ratio of £26,836 per quality adjusted life year.

Conclusions: While EndoPredict was found to be more expensive overall, the ability of the EPClin score to affect a more optimal allocation of chemotherapy, resulted in long term health gains. However, this result was on the margin of what is conventionally considered a cost-effective use of limited NHS resources and subject to significant uncertainty.

Clinical trial identification: ISRCTN69220108

Legal entity responsible for the study: Sussex Health Outcomes Research and Education in Cancer

Funding: Myriad

Disclosure: S. Hinde C. Theriou, S. May, L. Matthews, A. Arbon, L. Fallowfield, D. Bloomfield: This research was funded through an unrestricted educational grant from Myriad.

1126P The evolution of value with filgrastim in oncology

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Background: The value of drugs will evolve over time as new evidence for risks and benefits emerge and the price of a drug changes.

Methods: A NICE Evidence Search on March 1, 2017 revealed 25 systematic reviews and 55 economic evaluations of filgrastim.[1]

Results: Initial Health Technology Assessments (HTA) suggested low value due to high drug cost and no evidence for significant gain in Overall Survival (OS). More recent metanalyses of placebo-controlled randomized trial data show absolute OS gains of 3.2% (95% CI:2.1—4.2%) from filgrastim support of cytotoxic chemotherapy[2] and falling costs due to biosimilar competition.

Conclusions: Physicians and payers need to be aware that HTA decisions need constant re-evaluation, especially following the launch of biosimilar alternatives. This explains the first inclusion of filgrastim in the WHO essential Drug List for cancer more than 20 years after its original approval in 1991,[3] and demonstrates the power of biosimilar medicines in transforming healthcare. References [1] NICE Database search "filgrastim", performed March 1, 2017. URL: https://www.evidence.nhs.uk/search?q=filgrastim. [2] Lyman GH, Dale DC, Culakova E, et al. The impact of the granulocyte colony-stimulating factor on chemotherapy dose intensity and cancer survival: a systematic review and meta-analysis of randomized controlled trials. *Annals of Oncology*. 2013;24(10):2475-2484. doi:10.1093/annonc/mdt226. [3] WHO Model Lists of Essential Medicines, 19th Edition Reviewed November 2015.URL: http://www.who.int/medicines/publications/essentialmedicines/en/. Accessed March 1, 2017.

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1127P Tyrosine kinase inhibitors (TKI): Awareness of drug-drug interaction

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Background: Since TKI are metabolized with cytochrome P450 system which is a common pathway for drug-drug interactions. However, these interactions might be overlooked by clinicians. The aim of this study is to evaluate the drug-drug interactions in patients receiving TKI.

Methods: Between May 2007 and March 2015, the data of 265 patients receiving TKI for any reason were evaluated retrospectively. All prescribed medications (PMs) received during TKI therapy for 6 months period were noted and drug-drug interactions with TKI were evaluated. Additionally the nature of interaction was described as 'increase or decrease in TKI level or cautious use of TKI recommended'. The interaction between TKI and PMs was checked from Up-To-Date web site or "medscape.com/drug-interaction checker".

Results: In the study, 265 patients who are taking TKI were noted. 251 patients (94.8%) have been taking PMs additional to TKI. The median age was 56 year (17-87), most common diagnosis was gastrointestinal stromal tumor (27.5%) followed by kidney tumor (26.3%). Most common TKI has been used was Imatinib (21.9%) and Lapatinib (21.9%). The most common PM groups during 6 months period was non-steroidal anti inflammatory and acetaminophen (50.2%), proton pomp inhibitors (41.4%), antibiotics (33.1%), cardiovascular system drugs (33.5%) and narcotic analgesics (21.1%). The interaction rate between TKI and PMs was 54.2%. The nature of interaction was; decrease in TKI level in 39.7% of patients and increase in TKI level in 30.1% of patients. 77.1% of patients have been warned as cautious use of TKI due to increase risk of side effect. The side effect was emphasized as QT prolongation.

Conclusions: TKI drug interaction is usually overlooked by clinicians. Our study revealed that more than 90% of patients who are taking TKI are also prescribed another medication. There is a drug-drug interaction between TKI and prescribed medications in more than half of these patients. TKI-prescribed drug interaction has been caused decrease effectiveness of treatment and increase the rate of side effects and medical cost. The TKI –drug interaction risk might be decreased by increasing the knowledge of the physicians from other specialties about recent molecular treatments.

Legal entity responsible for the study: Ankara Numune Education and Research Hospital

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1128P Anti-PD1 inhibitors: Assessment of proper use, efficacy and economic impact in daily practice

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Background: Nivolumab, an anti-PD-1 inhibitor, has been approved in France in treatment of first-line BRAF wild-type advanced melanoma and of advanced non-small cell lung cancer after platinum-based chemotherapy, with an approximate monthly processing cost of €5,550 per patient. The objective of our study was to evaluate efficacy and correct use of anti-PD1 antibodies in daily practice since its approvals.

Methods: This retrospective study was conducted between July 2015 and December 2016 on 62 patient files at the Pitié-Salpêtrière hospital, using patient medical records and Multidisciplinary Medical Board (MMB) software. According to the Summary of Product Characteristics (SPC), the correct use of nivolumab required compliance with indications, a WHO status <2 and a limit of 10 mg per day of corticosteroids.

Results: Sixty patients were treated for lung cancer: 38 patients (62%) with adenocarcinoma, 14 (22%) with squamous cell carcinoma and 8 (13%) with large cell lung cancer. At the cut-off analysis, 28 patients (47%) had a progressive disease, 20 (32%) were still receiving treatment and 41(65%) were still alive, with a median follow-up of 6.5 months (0,3 to 17.7 months). Thirteen patients received more than 10 injections and 13 received less than 5 injections. The correct use of nivolumab was observed in 45 patients (73%), 12 patients had a WHO status of 2, 1 patient had a WHO status of 3, and 4 patients received concomitant corticosteroids. The poor utilization of treatment for these 17 patients (27%) totaled 149 injections, costing about €410,000 for a total of €1,615,000 of expenditures using this treatment. Survival rates were not statistically different in these patients compared to those respecting SPC criteria (53% versus 70%; $p = 0.2$).

Conclusions: Although a high cost of inappropriate use of nivolumab, there was no significant difference in survival rates in these patients. These preliminary findings highlight the differences between study populations and daily practice, reflecting willingness of practitioners to give patients access to innovative treatments. Cost effectiveness and efficacy/tolerance data will be updated at the meeting presentation to better determine treatment criteria in daily practice.

Legal entity responsible for the study: Assistance Publique - Hôpitaux de Paris

Funding: None

Disclosure: J-P. Spano: Received fees and has been member of advisory board of Bristol-Myers Squibb, MSD and Roche. All other authors have declared no conflicts of interest.

1129P Real world treatment costs and resource utilization among patients with metastatic bladder cancer

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Background: First-line (1L) cisplatin, followed by second-line (2L) taxane or other systemic chemotherapy, has been the historic standard of care in metastatic bladder cancer (mBC). Little is known regarding longitudinal costs and resources consumed during treatment of mBC patient (pts). This study investigated drug utilization, health care (HC) resource use, and disease-related costs among pts with mBC.

Methods: Pts with an initial diagnosis of mBC between Jan 2007 - Dec 2011 were retrospectively identified using SEER-Medicare linked data. Annual survival rates were calculated for treated and untreated pts. Total costs were estimated during the treatment exposure window for HC visits and treatment for mBC-related, AE-related, and other costs; all costs were converted to 2016 US dollars.

Results: Overall, 411 eligible pts received 1L therapy and 189 (46.0%) subsequently received 2L therapy. For all 1L treated pts, the 1, 2, and 3-year survival rates from mBC diagnosis were 56.5%, 25.6%, and 15.5%, compared to 12.9%, 6.0%, and 4.7% for untreated pts (n = 804). For 2L pts, the 1, 2, and 3-year survival rates from 2L treatment initiation were 32.8%, 14.9%, and 7.7%. For all regimens, the highest per-patient cost occurred in the outpatient setting, followed closely by emergency, then inpatient, SNF, and lastly by hospice.

Conclusions: In general, mBC pts had poor survival outcomes, particularly for untreated pts. Less than half of mBC pts received guideline-endorsed 1L cis-combo therapy. mBC-related outpatient and emergency HC utilization were primary drivers of the per-patient economic burden. During the treatment exposure window, total costs were considerable across treatment regimens, with the average total cost during 1L and 2L treatment exceeding sixty thousand dollars per patient.

Legal entity responsible for the study: Merck Sharp & Dohme Corp., Whitehouse Station, NJ, USA provided funding for this study, yet the authors take full responsibility for the work as a whole, including the study design, access to data reported in the manuscript, and the decision to submit and publish the manuscript. All authors approved the final manuscript to be published.

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Table: 1129P Costs Incurred During the Treatment Exposure Window for 1L and 2L mBC Therapies

Outcome	Treatment Group							
	Overall		Cisplatin-based regimen		Carboplatin-based regimen		Non-platinum-based regimen	
	1L	2L	1L	2L	1L	2L	1L	2L
Sample size, n (%)	411 (100%)	189 (100%)	162 (39.4%)	22 (11.6%)	185 (45.0%)	71 (37.6%)	64 (15.6%)	95 (50.8%)
Total cost per patient, mean (SD)	$36,793 ($28,754)	$26,732 ($21,143)	$35,570 ($25,770)	$25,267 ($16,494)	$38,751 ($29,864)	$30,279 ($23,298)	$34,228 ($32,509)	$24,443 ($20,233)
mBC-related cost per patient, mean (SD)	$18,246 ($16,655)	$12,939 ($13,340)	$19,316 ($16,660)	$13,529 ($11,872)	$18,769 ($16,667)	$14,980 ($16,837)	$14,028 ($16,213)	$11,294 ($10,304)
AE-related cost per patient, mean (SD)	$7,629 ($12,399)	$4,988 ($9,471)	$6,240 ($10,814)	$4,170 (6,473)	$8,503 ($11,931)	$5,374 ($7,345)	$8,618 ($16,663)	$4,889 ($11,324)
Other costs per patient, mean (SD)	$12,990 ($16,906)	$10,363 ($14,753)	$11,900 ($15,817)	$7,992 ($6,823)	$13,708 ($17,587)	$11,468 ($16,895)	$13,673 ($17,670)	$10,090 ($14,416)

1130P Investigating discrepancies in assessments of PFS by study investigators and independent review

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Background: OS is considered the gold standard trial endpoint, particularly for health technology assessment. However OS faces challenges – from subsequent therapy bias to needing long trials that delay patients' access to promising medicines. PFS is often used either instead of, or alongside, OS – by regulators, clinicians, payers, and more recently, value frameworks in oncology. PFS is without a standardized measure. We examine the extent of differences between independent central review (ICR) and investigator assessed (INV) PFS. We aim to increase understanding of potential variability in PFS measurement, relevant associations and possible causal factors to inform appropriate use of PFS in payer and clinician decision-making.

Methods: We searched Clinicaltrials.gov for 'progression free survival' and 'cancer', filtering for interventional phase 2 or 3 studies with results. Studies were extracted and the primary and secondary outcomes filtered for ICR and INV based PFS. We searched PubMed with the same criteria; full articles were reviewed and studies reporting for ICR and INV based PFS included. For comparative trials, we calculated difference in median PFS between intervention and control arms for ICR and INV based PFS. For single arm trials, the difference between ICR and INV based PFS was calculated where both were reported.

Results: Of 365 studies from clinical trials.gov; 48 reported ICR based PFS and 45 reported INV. 6 studies reporting both were included. Of 49 studies from PubMed; 21 were included. There was 1 duplicate. The majority of studies were comparative (23/26), in solid tumors (21/26), and published in the last 5 years (21/26).

Calculating the PFS gain at the median, the difference between the ICR based gain and the INV based gain ranged from 0.1 to 4.3 months. In 9 comparisons the gain with ICR

was greater than the gain with INV. In 6 comparisons the difference in PFS gain was ≥2 months, a difference of up to 54% of the gains alone.

Conclusions: ICR and INV based PFS produce different estimates of PFS gain in clinical trials, but it remains uncommon for studies to report both ICR and INV based PFS. Both measures should be required, to improve consistency of comparison across trials and transfer of trial results to real world practices and decision-making.

Legal entity responsible for the study: PRMA Consulting Ltd

Funding: PRMA Consulting

Disclosure: C.F. Jones, J.F. Soto Barrientos, G. Monnickendam: Employee of PRMA Consulting who sponsored this research.

1131P Medical costs and health care resource use (HCRU) in elderly us patients (pts) with newly diagnosed metastatic or surgically unresectable urothelial carcinoma (mUC) using surveillance, epidemiology, and end results (SEER) medicare data

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Background: Most elderly mUC pts receive platinum-based therapy as first line of treatment (LOT) but invariably progress, requiring additional LOT and HCRU. This analysis estimated medical costs and HCRU associated with each LOT in US elderly pts.

Methods: Pts ≥66 years of age newly diagnosed with mUC (urothelial transitional cell carcinoma) between 2004 and 2011 were identified from the SEER-Medicare database. Pts were followed from diagnosis to death, Medicare disenrollment, HMO enrollment, or till 31 December 2013 to characterize treatments by LOT (first [1L], second [2L], and third + [3L+] LOT). The per-pt HCRU was examined. Cumulative mean costs (overall and by type of LOT) were reported.

Results: Among 1,873 eligible mUC pts (median age, 77 years; male, 63%; Charlson comorbidity index ≥2, 29%; median follow-up, 7.5 months), 1,035 (55%) pts did not receive any chemotherapy. Among the 838 chemotherapy-treated pts, 510 (61%), 204 (24%), and 124 (15%) received 1L, 2L, and 3L+ LOT, respectively. Compared with 2L, 3L+ pts had significantly higher mean (standard deviation) per-pt hospital admissions (4.1 [2.9] vs 4.8 [3.3]), computed tomography (CT) scans (7.4 [4.4] vs 9.9 [5.8]), positron emission tomography–CT scans (1.0 [1.5] vs 2.0 [2.9]), and bone scans (1.1 [1.1] vs 1.8 [2.3]). Pts who received 3L+ LOT had significantly higher cumulative mean costs than 2L pts, mostly attributed to physician and outpatient services where chemotherapy is administered (Table).

Conclusions: For pts with mUC, cumulative mean costs increased with additional LOT, although further analysis of cumulative costs over the treatment duration of each LOT is warranted. As the treatment landscape evolves to include immunotherapy, this analysis provides a benchmark for the relative costs associated with mUC treatment across different traditional LOT in the United States.

Legal entity responsible for the study: Bristol-Myers Squibb

Funding: Bristol-Myers Squibb

Disclosure: A. Aly: Reports grants from Bristol-Myers Squibb, during the conduct of the study; grants from Bristol-Myers Squibb, Celldex, Celgene, Daiichi Sankyo, Pharmacyclics, and Amgen, outside the submitted work. C. Johnson: Reports grants from Bristol-Myers Squibb, during the conduct of the study. S. Yang, S. Rao: Reports personal fees from Bristol-Myers Squibb, during the conduct of the study; personal fees from Bristol-Myers Squibb, outside the submitted work. M. Botteman: Reports grants from Bristol-Myers Squib, during the conduct of the study; grants from Bristol-Myers Squib, Celgene, Celldex, Shire, outside the submitted work; and is an employee and owner of Pharmerit International. A. Hussain: Served as a consultant for Bristol-Myers Squibb.

1132P Chasing the survival curve tail: The effect on cost-effectiveness of nivolumab for second-line treatment of advanced renal cell carcinoma

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Background: Treatment of metastatic cancer has been revolutionized in recent years with the incorporation of immunotherapy. In some metastatic settings there is a clear plateau in the overall survival curve, representing long-term survivors. As survival data is still immature with immunotherapy in most cancers it is unclear how to tackle the unknown tail of the survival curve, as it greatly affects the presumed effectiveness. To further understand this issue we present here the example of CEA of nivolumab in 2nd line RCC.

Methods: A Markov model was developed to compare the costs and effectiveness of nivolumab with those of everolimus or placebo in the second-line treatment of advanced RCC. Health outcomes were measured in life-years and quality-adjusted life-years (QALYs). Drug costs were based on Medicare reimbursement rates in 2016. Model robustness was addressed in univariable and probabilistic sensitivity analyses. We examined the effect of different anticipated ends of the survival curve on the cost effectiveness.

Results: The total mean cost per-patient of nivolumab versus everolimus was $101,070 and $50,935, respectfully. Nivolumab generated a gain of 0.24 LYs (0.34 QALYs) over everolimus and 0.89 LYs (0.96 QALYs) over placebo. The incremental cost-effectiveness ratio (ICER) for nivolumab was $146,532/QALY versus everolimus. A theoretical durable response in 10%, 15% or 20% of patients treated with nivolumab reduced the ICER to $86,660/QALY, $64,809/QALY or $48,493/QALY, respectively, compared with everolimus.

Conclusions: Our analysis shows that any durable response changes the ICER dramatically and improves the likelihood that a drug will be considered cost effective. Therefore, we must thrive to understand the long term benefit of immunotherapy in different cancers.

Legal entity responsible for the study: Michal Sarfaty

Funding: None

Disclosure: All authors have declared no conflicts of interest.

Table: 1131P Cumulative per-patient costs from 3 months before diagnosis to end of follow-up (% total)

Cost category	All patients (N = 1,873)	No chemotherapy (N = 1,035)	1L only (N = 510)	2L only (N = 204)	3L + (N = 124)	*P-value* (3L+ vs 2L)
Median follow-up time, months	7.5	3.8	11.8	16.1	26.5	
Mean costs (%), $US	82,912 (100)	57,208 (100)	99,422 (100)	123,262 (100)	162,549 (100)	<0.001
Inpatient	43,990 (53)	36,840 (64)	51,358 (52)	54,698 (44)	55,575 (34)	0.359
Physician (incl. chemo for treated pts)[a]	21,426 (26)	10,087 (18)	26,735 (27)	39,955 (32)	63,476 (39)	<0.001
Outpatient (incl. chemo for treated pts)[b]	9,189 (11)	3,367 (6)	12,199 (12)	18,626 (15)	29,742 (18)	<0.001
Home health	2,631 (3)	2,042 (4)	3,256 (3)	3,018 (2)	4,329 (3)	0.166
Hospice	3,208 (4)	3,624 (6)	2,337 (2)	2,671 (2)	4,211 (3)	0.208
Durable medical equipment	1,117 (1)	550 (1)	1,771 (2)	1,627 (1)	2,303 (1)	0.849
Prescription drugs (not incl. chemo)	1,351 (2)	698 (1)	1,767 (2)	2,668 (2)	2,912 (2)	0.652

[a]Physician costs are non-institutional claims largely from physicians who bill for services provided in the office

[b]Outpatient costs are claims from institutional outpatient providers

1133P Non-elective admissions in cancer care - A review of acute oncology services (AOS) implementation in a north-west region of England

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Background: Parallel to advances in cancer therapeutics in the clinics, high quality and patient-centred management of cancer or treatment-related complications during non-elective attendance especially to a non-specialist hospital is crucial in achieving excellent patient outcome. AOS was innovated in the UK to meet this need and has rapidly expanded in recent years. Here, we describe findings of an on-going audit of this expanding networked service within Greater Manchester and Cheshire East County consisting of 10 district general hospitals in collaboration with a regional specialist cancer centre (The Christie NHS Foundation Trust).

Methods: Information related to any hospital episodes warranting AOS input was collated from all participating hospitals using standardised proforma and analysed.

Results: Between Jan 2015 - Sep 2016, 7638 non-elective hospital attendances were recorded of which 58% occurred within working hours. Common cancer sites were lung 16%, breast 15%, lower GI 12%, urology 12%, upper GI and HPB 9%, haematology 7%, gynaecology 6%, cancer of unknown primary(CUP) 6%, and others 7%. Majority were related to cancer complication 40% (Type III), treatment - related 32% (Type II), new cancer diagnosis 10% (Type I) and others 17%. 94% of AOS involvement occured within 24hr of attendance. Level of intervention by AOS was considered major in 60% while 30% and <10% was intermediate or minor respectively. Median length of stay (LOS) is 4 days, 20% of episodes lasted <24hr (11.2% admission avoidance), 50% 1-7 days, and 30% 2-6 weeks (predominantly type I and III).

Conclusions: This large multi-sites audit documented the service delivery pattern of a growing oncology subspecialty at the same time provided a glimpse into the healthcare implication of unplanned admission in the current era of advancing oncology lanscape. Excellent median LOS in this region compared to national average likely a reflection of pertinent AOS team involvement in a timely manner. AOS is now an integral component to the cancer care in the UK and its role in the non-elective setting serves to ensure excellent patient experience as well as providing far-reaching potential in healthcare efficiciency.

Legal entity responsible for the study: not applicable

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1134P Changing treatment patterns in metastatic colorectal cancer in EU5 countries from 2014 to 2016

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Background: Colorectal cancer is the third most common cancer type nowadays in Europe. Lately however, no treatment has been approved for 1st or 2nd line treatment in metastatic colorectal cancer, only a new treatment option in 3rd line for pretreated patients is available. Therefore it will be interesting to see whether also the existing treatment patterns and testing results have not changed over time.

Methods: This study is based on IMS Oncology Analyzer®, a quarterly survey among a physician panel covering retrospective patient data about the disease and the treatment (tx) history across all types of cancer. Metastatic colorectal cancer patients treated in the EU5 countries (France, Germany, Spain, Italy and UK) within 2014, 2015 and 2016 were analyzed.

Results: Comparing the tx guidelines to the tx patterns derived from IMS Oncology Analyzer®, it shows that physicians are following the guidelines for K-RAS wildtype and K-RAS mutant colorectal cancer patients. An analysis of the K-RAS testing shows, that the share of wildtype patients remains almost stable from 2014 to 2016. Unlike in Germany, here the shares of wildtype patients are shrinking from 57.2% to 51.3%. A similar trend accounts for UK. In Spain, France and Italy however, the number of patients, who are wildtype is increasing. Accordingly to the decreasing rate of wildtype patients, the share of Anti-EGFR-therapies is going down in Germany from 38.8% to 25.3%. Also in Italy and Spain the trend of the K-RAS testing is mirrored in the usage of Anti-EGFR-therapies. However, in UK, the use of these therapies increases drastically from 23.9% to 77.8%, despite the decreasing number of K-RAS wildtype patients. In France Anti-EGFR-therapies only lose 1.7% in terms of market shares, even though the K-RAS wildtype population is increasing.

Conclusions: While the general tx guidelines are still followed, some tx patterns have changed due to a difference in K-RAS test results. Further research needs to investigate why there are changes in K-RAS test results. Also studies have shown that tumor localization (right, left, transversum) has an impact on the efficacy. Future studies therefore need to evaluate whether the tumor localization is impacting the tx pattern as well.

Legal entity responsible for the study: QuintilesIMS

Funding: None

Disclosure: All authors have declared no conflicts of interest.

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

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IMMUNOTHERAPY OF CANCER

1144O Phase III randomized controlled trial of adjuvant chemoimmunotherapy in patients with resected primary lung cancer

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Background: Adoptive cellar immunotherapy is not widely approved as a treatment option for cancer treatment. The preliminary results from our phase III, randomized controlled trial (RCT) of adjuvant chemoimmunotherapy for lung cancer indicated significant advantages in patients receiving immunotherapy. Here we report the final results and long-term analysis of this RCT.

Methods: A hundred and three postsurgical non-small-cell lung cancer patients were randomly designated to receive either chemoimmunotherapy (group A, immunotherapy arm, n = 51) or chemotherapy (group B, control arm, n = 52). The immunotherapy consisted of adoptive transfer of autologous activated killer T cells and dendritic cells obtained from regional lymph nodes of the patients.

Results: The 2- and 5-year overall survival (OS) rates were 96·0% and 69.4% in group A and 64·7% and 45.1% in group B, respectively. The hazard ratio (HR) was 0.451 (0.235∼0.807) by multivariate analysis. The 2- and 5-year recurrence-free survival rates were 70.0% and 57·9% in group A and 43.1% and 31.4% in group B, respectively. P values of Log-rank test between groups were 0.0059. Subgroup analysis for the OS between treatment groups indicated males (HR, 0·474), adenocarcinoma patients (HR, 0·479), stage III cancer patients (HR, 0·399), and those who did not receive preoperative chemotherapy (HR, 0·483) had lower HRs than those in the other groups. Immunological analysis of cell surface markers in regional lymph nodes of subjects receiving immunotherapy indicated that the $CD8^+/CD4^+$ T-cell ratio was elevated in survivors.

Conclusions: Non-small-cell lung cancer patients benefited from adoptive cellular immunotherapy as an adjuvant to surgery. Immunological analysis of cell surface markers indicated cytotoxic T cells were essential for a favorable chemoimmunotherapy outcome.

Clinical trial identification: The University Hospital Medical Information Network in Japan (UMIN: 000007525).

Legal entity responsible for the study: Chiba Cancer Center, Japan

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1135O Phase 1b/2 Study (SCORES) assessing safety, tolerability, and preliminary anti-tumor activity of durvalumab plus AZD9150 or AZD5069 in patients with advanced solid malignancies and squamous cell carcinoma of the head and neck (SCCHN)

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Background: Anti-tumor activity of durvalumab (D), a programmed death ligand (PDL1) blocking antibody, may be enhanced by overcoming intratumoral immune suppression. The selective Generation 2.5 antisense oligonucleotide STAT3 inhibitor AZD9150 (STATi), a small molecule CXCR2 inhibitor AZD5069 (CX2i), and CTLA4 inhibitor tremelimumab (T) are in evaluation.

Methods: Part A, dose escalation in solid tumors, evaluated STATi + (D or D+T) and CX2i + (D or D+T) for safety, pharmacokinetics, pharmacodynamics and maximum tolerated dose. Part B, dose expansion in SCCHN, tested STATi (3 mg/kg)+D and CX2i (40 mg BID)+D in PDL1 pretreated/naive pts and as monotherapy for Objective Response Rate (ORR) and Disease Control Rate (DCR).

Results: Part A showed STATi+D and CX2i+D as safe and tolerable combinations with confirmed partial responses (cPR) in multiple tumor types and 2 confirmed complete responses (cCR) in breast and prostate cancer (>64 weeks [wks] on treatment). STATi+DT had a cPR in sarcoma at 12 wks. In Part B (STATi+D reported here), the PDL1 naive arm had 25% ORR (4 cPR, 1 unconfirmed PR (uPR); 3 Human Papilloma Virus negative and 2 unknown), 45% DCR (9/20) was observed at 12 wks, and 30% of pts (6/20) remain on treatment at 25 wks. One cPR pt is unconfirmed CR at data cut off. In the PDL1 pretreated arm, 1 pt had complete metabolic response and 1 pt had uPR; 20% DCR (3/15) was observed at 12 wks. Safety and tolerability were confirmed for STATi+D in SCCHN pts, with manageable and reversible adverse events of thrombocytopenia and liver enzyme increases (for each, Grade 3/4 in 3.4% of 58 pts dosed); 2 STATi+D related discontinuations occurred.

Conclusions: Initial ORR and DCR data suggest enhanced antitumor activity results from combining a PDL1 antagonist (D) with an agent targeting immunosuppression in the tumor microenviornment (STATi) compared to PDL1 monotherapy. The combination may prove to provide a tolerable and effective option for patients with recurrent/metastatic SCCHN in the naive and PDL1-pretreated setting and other solid tumor types being studied.

Clinical trial identification: NCT02499328

Legal entity responsible for the study: AstraZeneca PLC

Funding: AstraZeneca

Disclosure: E.E. Cohen: Consulted for AstraZeneca, Bristol-Myers Squibb, Human Longevity, Merck, Merck Serrano, and Pfizer. Received expenses for travel or accommodation from AstraZeneca, Merck, and Pfizer. Holds stock in Human Longevity, Inc. D.S. Hong: Received grants from Bayer, Lilly, Genentech, LOXO, Pfizer, Amgen, Mirati, Ignyta, Merck, Daichi-Sanko, and Eisai. Travel expenses were provided by MiRNA and LOXO. Consulted for Bayer, Baxter, and Guidepoint Global. He founded Oncoresponse. T. Wise Draper: Received funding for investigator-initiated studies from Bristol-Myers Squibb and Merck. D. Schrijvers: Participated in studies sponsored by Cougar, Janssen, and Bayer. Served on the advisory board of Janssen and Bayer Belgium. Spoken at events organized by Janssen and Bayer Belgium. R. Mesia Nin: Served an advisory role for AstraZeneca, Merck SL, Bayer, and Bristol. Received conference honoraria from Bristol and Merck SL. M.L. Scott, P. Lyne, P. McCoon, C.E. Cook: Employee of, and owns stock in, AstraZeneca. G. Mugundu: Employee of AstraZeneca and owns stock in AstraZeneca and Pfizer. M.M. Mehta: Employed by AstraZeneca. U. Keilholz: Received speaker honoraria, and served on advisory boards, for AstraZeneca, Merck, MSD, Pfizer, Novartis, and Innate. Participates in research sponsored by AstraZeneca and Merck. All other authors have declared no conflicts of interest.

1136O Nivolumab and ISA 101 HPV vaccine in incurable HPV-16+ cancer

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Background: Vaccines directed against Human Papilloma Virus (HPV) do not generally mediate regression of invasive cancer. To test the hypothesis that the efficacy of vaccine-induced T cells may be amplified through treatment with immune checkpoint antibodies, we conducted a phase II trial of ISA 101, a synthetic long-peptide HPV-16 vaccine, and nivolumab in pts with incurable HPV-16+ cancer.

Methods: Tumors were HPV-genotype 16 by Cervista HPV16/18. Patients were ECOG PS 0-1 with up to one prior regimen for recurrence. ISA101 100 mcgs/peptide was given Days 1, 22, 50. Nivolumab 3 mg/kg was given iv every 2 wks beginning day 8 for up to one year. Imaging was obtained baseline, 11 wks and every 6 wks thereafter. The primary objective was assessment of overall response rate (ORR) targeting 30%. Secondary objectives: tolerability, PFS, OS. A Simon two stage design required response in 2/15 first stage and 5/25 in second stage.

Results: The trial accrued 24 patients; 22 with oropharynx cancer (OPC) and 1 pt each with anal and cervical cancer. 18 pts (75%) had progression within 6 mos of prior platin and 1 was platin-naïve. 12 pts (50%) had prior cetuximab. Treatment was frontline for recurrence in 10/24 and second line in 14/24. ORR is 33% (8/24): 1 CR, 7 PR (1 unconfirmed), 3(13%) SD, 13 (54%) PD. ORR in OPC pts is 36% (8/22). 6/8 pts with PR progressed within 6 mos of prior platin. Median duration of response 30.1+ wks (6- 49+ wks); 5/8 pts with PR remain in response. Median PFS is 2.7 mos [95% CI 2.3-8.0 mos] and median OS is not reached with median follow up time among censored pts 8.6 mos. PFS rate at 6 mos: 33%, [16-52%] OS rate at 6 mos 74%, [51-87%] . Toxicity:

grade 3 transaminase and grade 4 lipase elevation in 1 pt each, grade 1-2 toxicity: fever (5 pts), injection site reaction (6 pts), transaminase elevation, fatigue, nausea (3 pts each).

Conclusions: The primary endpoint was met and ORR of 36% in OPC pts compares favorably to 16% for nivolumab monotherapy in p16+ OPC pts in Checkmate 141 (Ferris RL et al N Engl J Med 2016; 375:1856). These data suggest that the efficacy of vaccine-induced T cells can be augmented by anti-PD-1 therapy, mitigating the influence of an immunosuppressive microenvironment. Our findings merit confirmation in a larger randomized trial. Correlation of efficacy outcomes with immunoprofiling of tumors will be presented.

Clinical trial identification: NCT02426892

Legal entity responsible for the study: U T M D Anderson Cancer Center

Funding: U T M D Anderson Cancer Center

Disclosure: S. van der Burg, C. Melief: Employed by ISA Pharmaceuticals Inc. All other authors have declared no conflicts of interest.

1137O Interim analysis of the phase 3 ADAPT trial evaluating rocapuldencel-T (AGS-003), an individualized immunotherapy for the treatment of newly-diagnosed patients with metastatic renal cell carcinoma (mRCC)

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Background: Rocapuldencel-T is an investigational immunotherapy formulated with RNA isolated from the patient's tumor to program autologous dendritic cells with tumor-specific antigens. It is administered chronically via intradermal injection to activate a tumor-specific memory T-cell response.

Methods: The Phase 3 ADAPT trial was designed to evaluate overall survival (OS) of rocapuldencel-T in combination (Combo) with standard-of-care (SOC) for the treatment of newly diagnosed mRCC as compared to SOC alone (Control). It included adults with synchronous, clear cell mRCC who were eligible for nephrectomy at 107 sites across North America, Europe and Israel.

Results: 462 patients were randomized 2:1 from February 2013 - October 2015. In February 2017, an interim analysis by the Independent Data Monitoring Committee after 75% of the targeted number of 290 events (deaths) prompted a recommendation to stop the trial because the OS hazard ratio was greater than the pre-defined futility boundary (0.98) for the 3rd interim assessment. However, in consultation with investigators and the FDA, the sponsor has continued the trial due to the still maturing survival data, the mechanism of action of rocapuldencel-T, which involves the induction of long-term memory immune responses, and its' safety profile. The median duration of follow-up was 20 months and more than half the patients in both treatment groups were still alive. Data from the first third of patients randomized (n = 154), and, therefore the longest follow up time and least censored data (44%), suggest a potential survival benefit for the combination worthy of further assessment. Additionally, a statistically significant correlation was observed between the increase in the number of rocapuldencel-T induced memory T cells (CD8+/CD28+/CD45RA-) and OS in patients for whom data has been analyzed and 7 doses of rocapuldencel-T has been administered (n = 114). Updated long-term response and immune data will be presented.

Conclusions: The ADAPT trial is ongoing to further assess the long-term effects of this well-tolerated individualized immunotherapy.

Clinical trial identification: NCT01582672

Legal entity responsible for the study: Argos Therapeutics

Funding: Argos Therapeutics

Disclosure: R. Figlin: Institution receives research funding. C. Nicolette, M. Debenedette, T. Monesmith, W. Tan, S. Leland: Employee of Argos Therapeutics. N. Tannir: Grants and/or personal fees and non-financial support from Bristol-Myers Squibb, Exelixis, Nektar, Pfizer, Argos, Calithera, Epizyme, Miranti, outside the submitted work. All other authors have declared no conflicts of interest.

1138PD Immune checkpoint inhibitor (ICPI) efficacy and resistance detected by comprehensive genomic profiling (CGP) in non-small cell lung cancer (NSCLC)

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Background: The prediction of outcome to ICPI in advanced NSCLC is of great clinical interest. We considered CGP, PD-L1 IHC, and real world data to investigate potential biomarkers for ICPI response.

Methods: CGP and IHC was performed on 1,619 FFPE NSCLC samples in the FoundationCORE database (FMI). The SP142 antibody was used to capture PD-L1 tumor expression (PD-L1 TE) for these 1,619 samples. NSCLC patients (n = 2139) in the Flatiron Health Analytic Database with FoundationOne testing CGP results and real world IHC results for PD-L1 TE were analyzed separately (FMI-FIH). CGP used ≥50 ng of DNA and a hybrid-capture, adaptor ligation-based assay (median coverage depth >600X). TMB (mut/Mb) was determined on 1.1 Mb of sequenced DNA.

Results: PD-L1 IHC TE correlated weakly with TMB (FMI samples) (Spearman's ρ 0.085, p = 6.16e-4); mean TMB was 10.9 mut/Mb, median 8.1 mut/Mb and 14.5% had high TMB (≥20 mut/Mb). From FMI-FIH, high TMB but not PD-L1 status predicted longer mean duration on therapy (DOT) (p = 0.001). Analysis of the FMI and FMI-FIH datasets revealed relationships between GA, PD-L1 TE, TMB, and mean DOT. Inactivating *STK11* GA were seen in 12.1% of FMI-FIH and 15.1% of FMI samples, most often adenocarcinomas (aCa). *STK11* GA correlated with high TMB/low PD-L1 (FMI; p = 0.0014) and preliminary analyses suggest correlation with negative ICPI treatment outcome. Several genes were commonly co-altered with *STK11* (FMI): *KRAS* (54.5%), *TP53* (43%), *CDKN2A* (27.5%), *CDKN2B* (20.1%), *KEAP1* (18.9%), and *MYC* (13.5%). *BRAF* GA, most often short variants (SV) in aCa, were associated with prolonged DOT on ICPI regardless of TMB score (FMI-FIH; p = 0.0073). *MET* SV also predicted prolonged DOT on ICPI, but insufficient events prevented calculation of statistical significance (FMI-FIH). Analysis of the TCGA lung aCa dataset revealed *MET* SV (2.8%) linked with immune activation gene expression profiles ($p < 0.05$) and *STK11* mutations (14.2%) with immune evasion profiles ($p < 0.05$).

Conclusions: Although TMB powerfully predicts ICPI outcome independent of tumor cell PD-L1 expression, considering GA in STK11, BRAF or MET may significantly increase the precision and improve outcomes when using genomics with IHC to guide to ICPI selection.

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

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1139PD Analyzing biomarkers of cancer immunotherapy (CIT) response using a real-world clinico-genomic database

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Background: Highly discriminating biomarkers of response to cancer immunotherapies (CIT) remain elusive. Characterization of large real-world populations treated with CIT as part of routine care may enable better stratification.

Methods: Patients in the Flatiron Health Analytic Database with non-small cell lung cancer (NSCLC) who underwent comprehensive genomic profiling (CGP) by Foundation Medicine were included (n = 2139). CGP included >300 genes and tumor mutation burden (TMB), stratified into low (TMB-L; <6 mut/MB), intermediate (TMB-I; 6-20 mut/MB), and high (TMB-H; > =20 mut/MB) tertiles (Johnson, CIR 2016). PD-L1 expression was obtained from results reported to clinicians from multiple labs (using varying antibodies). Genomic data was linked to de-identified electronic health record (EHR) data, from which nivolumab response was measured as overall response rate (ORR = SD, PR, or CR), median duration of therapy (mDOT), and median overall survival (mOS) from advanced diagnosis and from nivolumab initiation.

Results: In patients treated with nivolumab (n = 444, 20.8%), TMB-H predicted longer mDOT than TMB-L/I (7.5 vs 4.6 months, p = 0.001), mOS from start of nivolumab treatment (median not reached vs 10 months, p < 0.01), and mOS from advanced diagnosis (65 vs 29 months, p = 0.10). In contrast, PD-L1 status (n = 282) was not associated with ORR, DOT, or OS. Among patients negative for PD-L1, TMB-H predicted longer DOT (mDOT 391 vs 166 days, p = 0.08) and higher ORR (100% in TMB-H [n = 5] vs 62% in TMB-I/L [n = 28], p = 0.03). TMB remained predictive of DOT and OS from nivolumab start when controlled for histology, age, stage, smoking, gender, and race in multivariate analysis. Multivariate analysis of TMB-L patients identified two additional genomic predictors of duration on nivolumab: BRAF (HR 0.12, p = 0.04), and BRCA 1/2 (HR 0.05, p = 0.01).

Conclusions: Real-world datasets combining clinical outcomes with genomic profiling may enable biomarker discovery in CIT. These data demonstrate the predictive power of TMB, which can augment and significantly improve on the currently approved PD-L1 expression as a predictor of CIT response. They may also enable discovery of novel biomarkers that can identify potential CIT responders among TMB-L populations.

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

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1140PD Predictive biomarkers for hyper-progression (HP) in response to immune checkpoint inhibitors (ICI) – analysis of somatic alterations (SAs)

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Background: Pseudo-progression associated with ICI has been well described. HP - characterized by paradoxically accelerated tumor growth rate (TGR) - while on ICI is increasingly being recognized. Preliminary data have reported murine double minute (MDM2/MDM4) amplification as a possible predictive biomarker for HP based on pre-treatment next generation sequencing (NGS) of tumor tissue. We sought to identify patients that hyper-progressed at our institution, characterize the SAs in those patients (pts) and conversely, estimate the incidence of HP in pts with such SAs.

Methods: HP was defined as: 1. progression at first restaging on ICI 2. Increase in tumor size > 50%, 3. >2-fold increase in TGR. Data were obtained by interrogating our institutional electronic medical record and molecular database (MDB). Next Generation Sequencing (NGS -Foundation Medicine, Cambridge MA) was performed on pre-treatment tumor tissue; DNA was extracted, NGS was performed on hybrid-capture, adaptor ligation based libraries to a mean coverage depth of > 600 for up to 315 genes plus 47 introns from 19 genes frequently rearranged in cancer.

Results: 5 pts met criteria for HP, NGS data was available on 4 (80%) pts. Most frequently encountered SAs were MDM2/MDM4 amplifications (amp -50%), EGFR amp (25%) and amp of several genes located on chromosome 11q13 -CCND1, FGF3, FGF4, FGF19 (75%). Tumor mutational burden ranged from 4-13/Mb for all pts with HP. Review of our MDB (N = 696) identified MDM2/MDM4, EGFR and 11q13 amp in 26 (4%), 26 (4%) and 25 (4%) pts respectively. Of the 70 patients with these SAs, 10 received ICI. The incidence of HP in pts with MDM2/MDM4, EGFR and 11q13 amp was 2 (66%), 1 (50%) and 3 (43%) respectively. Patient details are summarized below.

Conclusions: A subset of pts treated with ICI develop HP. Copy number alterations in MDM2/MDM4, EGFR and several genes located on 11q13 are associated with HP. The role of these SAs as putative predictive biomarkers for HP needs further validation in larger cohorts of pts. Immune escape/editing, leading to HP needs mechanistic elucidation; prospective identification of pts at risk for HP is crucial and merits further investigation.

Legal entity responsible for the study: Arun K Singavi, MD and Ben George, MD

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Disclosure: S. Ali: Employee - Foundation Medicine, Cambridge, MA. B. George: Consultant for Celgene, Cook Medical, Merrimack, Foundation Medicine, Ipsen. All other authors have declared no conflicts of interest.

1141PD CA-170, a first in class oral small molecule dual inhibitor of immune checkpoints PD-L1 and VISTA, demonstrates tumor growth inhibition in pre-clinical models and promotes T cell activation in Phase 1 study

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Background: Programmed-death 1 (PD-1) and V-domain Ig suppressor of T-cell activation (VISTA) are independent immune checkpoints that inhibit T cell function. Preclinical studies demonstrated that dual blockade of these checkpoints can be synergistic. CA-170 is an oral small molecule antagonist of PD-L1 and VISTA, currently undergoing Phase (Ph) 1 clinical testing.

Methods: Pre-clinically, CA-170 inhibition of PD-L1 or VISTA-mediated suppression of T cell function was tested *in vitro* using human, monkey, or mouse cells. *In vivo* anti-tumor activity was examined in multiple syngeneic mouse models. Pts with advanced solid tumors or lymphomas, age ≥ 18, ECOG ≤1 and adequate organ function are treated with escalating doses of oral CA-170 daily during Ph 1a. Ph 1b dose expansion will enrich enrollment for selected pt population possibly responsive to this novel inhibitor. Primary objectives: safety, maximum tolerated dose and recommended Phase 2 dose. Secondary objectives: pharmacokinetics and anti-tumor activity. Exploratory endpoints: biomarkers and pharmacodynamic (PD) effects in periphery and tumor tissues.

Results: CA-170 rescues *in vitro* T cell effector function with activity comparable to that of PD-1 or VISTA blocking antibodies. Oral CA-170 inhibits the growth of mouse syngeneic tumors (B16 melanoma, CT26 and MC38 colon carcinoma), enhances peripheral T cell activation, and promotes the activation of tumor infiltrating $CD8^+$ T cells *in vivo*. In humans, a total of 19 patients have been treated across 6 dose levels (50 - 800 mg). No dose limiting toxicity has been observed. CA-170 exhibits generally dose proportional plasma exposure with $T_{1/2}$ of ~ 4-9.5 hours. Evidence of peripheral T cell activation was observed with an increased proportion of circulating $CD8^+$ and $CD4^+$ T cells expressing activation markers, CD69 and CD134, following oral dosing.

Conclusions: These pre-clinical and preliminary clinical PD data warrant the continued clinical development of CA-170, the first oral, small molecule immune checkpoint antagonist for the treatment of advanced cancers. Dose escalation is currently ongoing (NCT02812875).

Table: 1140PD

Age - Sex	Disease	# Prior lines of chemotherapy	ICI	Time to HP (months)	NGS
65 - Male (M)	NSCLC	2	Nivolumab (N)	2	CCDN1, CDK4, FGF19, FGF4, MDM2, FGF3, FRS2
68 - M	Esophageal Adeno Ca	1	Pembrolizumab (P)	2	CCND1, EGFR, FGFR19, FGF3, FGF4,
77 - M	Esophageal SCC	3	P	3	EPHA3, MDM4, CHEK2, EP300, NOTCH1, NOTCH3, SPOP, TP53
59 - M	Lung Ca (neuroendocrine features)	1	N	2	CCND1, FGF19, FGF3, FGF4, KRAS, NFE2L2, TP53
58 F	Renal Cell Ca	2	N	1	NA

Clinical trial identification: NCT02812875

Legal entity responsible for the study: Curis Inc

Funding: Curis Inc

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1142PD Safety, pharmacokinetics (PK) and pharmacodynamics (PD) data from a phase I dose-escalation study of OX40 agonistic monoclonal antibody (mAb) PF-04518600 (PF-8600) in combination with utomilumab, a 4-1BB agonistic mAb

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Background: PF-8600 and utomilumab are fully human IgG2 agonistic monoclonal antibodies directed at tumor necrosis factor receptor superfamily receptors OX40 and 4-1BB, respectively. In general, OX40 has a greater impact on CD4 T cell function, while 4-1BB has more impact on CD8 T cell function. Dual targeting of OX40 and 4-1BB synergistically induced CD8 and cytotoxic CD4 T cell clonal expansion in pre-clinical models. A Phase I study (NCT02315066), evaluated PF-8600 alone and in combination with utomilumab. As seen previously for utomilumab alone, PF-8600 monotherapy was tolerable at all dose levels, providing rationale to combine PF-8600 with utomilumab.

Methods: Non-small cell lung cancer, head and neck squamous cell carcinoma, melanoma, bladder, gastric or cervical cancer patients (pts) unresponsive to available therapies or where no standard therapy is available are treated with PF-8600 at dose levels 0.1 mg/kg to 3 mg/kg q2w in combination with utomilumab at either 20 mg or 100 mg q4w intravenously. Blood was collected for PK/PD analysis.

Results: At time of data cut-off on 30-Jan 2017 (study ongoing), 28 pts had enrolled in 4/5 planned dose cohorts. No drug-related deaths, dose-limiting toxicities, or suspected unexpected serious adverse reactions have been confirmed to date. All drug-related adverse events (AEs) were grade (G) 1-2. The most common were nausea (10.7%), decreased appetite (7.1%) and fatigue (7.1%). Nine (32.1%) G3, 3 (10.7%) G4 and 2 (7.1%) G5 all-causality AEs were reported (G5 AEs in lowest dose cohort). Combination treatment resulted in greater increases in expression of activation and proliferation markers on CD8 memory T cells, in particular, and memory T cell subsets overall, than PF-8600 alone. Preliminary PK and efficacy data will be shown.

Conclusions: To date, dose escalation combining active monotherapy doses of PF-8600 and utomilumab has not demonstrated toxicity beyond that expected from either alone. Safety, efficacy, PK, and PD data from dose escalation will aid selection of optimal biologic doses for further evaluation and expansion.

Clinical trial identification: NCT02315066

Legal entity responsible for the study: Pfizer Inc

Funding: Pfizer Inc

Disclosure: O. Hamid: Consulting/Advising: Amgen, Novartis, Roche, Bristol-Myers Squibb, Merck; Speakers' Bureau Bristol-Myers Squibb, GNE, Novartis, Amgen; Research Funding (Institution): AstraZeneca, Bristol-Myers Squibb, Celldex, GNE, Immunocore, Incyte, Merck, Merck Serono, MedImmune, Novartis, Pfizer, Rinat, Roche. J.A. Thompson: Honoraria: Celledex Consulting or advisory role: Celledex Research Funding (to institution): Bristol-Myers Squibb Agensys Seattle Genetics Pfizer Trillium Therapeutics Merck Inc. S. Hu-Lieskovan: Consulting: Amgen, Merck, Novartis, Vaccinex, Emergent BioSolutions Contracted Research: Pfizer, Plexxikon, Genentech, Neon Research Support: Bristol-Myers Squibb, Merck Travel Support: Amgen, Merck, Novartis, Vaccinex, Emergent BioSolutions, Neon. F.A.L.M. Eskens: Consulting or Advisory Role: Daiichi Sankyo Ipsen Pfizer Merck Inc. Novartis Pharma KK Travel, Accommodations, Expenses Daiichi Sankyo Ipsen Roche-Peru. A. Diab: Consulting/advisory: Nektar, CureVac, Celgene Travel/accomodations/expenses: Nektar Research funding (to institution): Nektar, Idera, Celgene, Pfizer. T. Doi: Advisory: Lilly, Chugai, Kyowa Hakko Kirin, Nippon BI, Novartis, MSD, Daiichi Sankyo, Amgen Funding to institution: Taiho, Novartis, Merck Serono, Astellas, MSD, Janssen, BI, Takeda, Pfizer, Lilly, Sumitomo, Chugai, Bayer, Kyowa, Daiichi Sankyo, Celgene. J. Wasser: Have received research support from Pfizer by means of a material transfer agreement. J-P. Spano: Adboard with Pfizer (Breast cancer). N.A. Rizvi: Advisory Board: Merck, AstraZeneca, Roche, Bristol-Myers Squibb, Novartis, Pfizer, Lilly, Novartis, Abbvie Co-founder and shareholder: Gritstone Oncology Scientific Advisory Board: Nilogen Oncosystems. A. Chiappori: Participated in advisory boards for Genentech, Novartis, Bristol-Myers Squibb, ARIAD and have also received honoraria from Genentech, Merck, Celgene, Boehringer Ingelheim. Received honoraria from Pfizer too, but not within the last year. P.A. Ott: Grants to the institution and personal fees from Bristol-Myers Squibb, CytomX, Celldex, Pfizer and Merck, personal fees from Neon Therapeutics, Amgen, Novartis, and Roche/Genentech, and grants from AstraZeneca/MedImmune, outside of the submitted work. B.J. Ganguly, K. Liao, T. Joh, J. Chou, C. Fleener: Employee and stockholder of Pfizer Inc. V. Dell: Contractor for Pfizer. A. El-Khoueiry: Advisory: CytomX, Bristol-Myers Squibb, AstraZeneca Speakers Bureau: Merrimack Honoraria: Merrimack, Bayer, Novartis, Bristol-Myers Squibb. All other authors have declared no conflicts of interest.

1143PD Dose-finding combination study of niraparib and pembrolizumab in patients (pts) with metastatic triple-negative breast cancer (TNBC) or recurrent platinum-resistant epithelial ovarian cancer (OC) (TOPACIO/Keynote-162)

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Background: Platinum-resistant OC represents an unmet medical need with progression free survival (PFS) of 3.5 to 6 months. Niraparib, an oral PARP 1/2 inhibitor (PARPi), improved PFS in pts with recurrent OC following response to platinum (NEJM, 2016). Preclinical evidence suggests synergy between PARPis and PD-1 inhibitors in OC and TNBC. We report data from a phase 1 niraparib + pembrolizumab (pembro) combination study leading to recommended phase 2 dose (RP2D).

Methods: Primary objectives were to assess dose limiting toxicities (DLTs) in a 6 + 6 dose escalation design and determine RP2D. Eligible pts had metastatic TNBC treated with ≤4 prior lines of chemotherapy OR platinum-resistant recurrent OC treated with ≤5 prior lines of chemotherapy having responded with CR or PR for >6 months to 1st line platinum based chemotherapy.

Results: The 14 pts (≥18 yrs) enrolled received pembro 200 mg IV on day 1 and niraparib 200 mg (dose level [DL] 1, n = 7; 2 TNBC, 5 OC) or 300 mg (DL2, n = 7; 3 TNBC, 4 OC) PO on days 1–21 of each 21-day cycle. In DL1, 1 pt had DLTs (neutropenia, anemia and thrombocytopenia) and discontinued niraparib but continued pembro. In DL2, 1 pt had DLT and 1 had DLT-equivalent (both thrombocytopenia); both resumed treatment with 200 mg niraparib and continued pembro. RP2D was determined as niraparib 200 mg PO daily + pembro 200 mg IV on day 1 of each 21-day cycle. Based on RECIST v1.1, 4/8 evaluable OC pts responded; the other 4 pts achieved SD (Table). 1/5 TNBC pts (BRCA wildtype) had SD for 10 cycles. BRCA & PD-L1 status will be presented.

Table: 1143PD

Best response OC N = 8	Time to response[$] Cycle (weeks)	Time on study Cycle*
CR	3 (9)	11+
PR	6 (18)	9
PR	6 (18)	13+
PR	3 (9)	8
SD	2 (6)	3
SD	3 (9)	6
SD	3 (9)	5
SD	3 (9)	6

* + = ongoing

[$]Assessed every 3 cycles

Conclusions: This study established a RP2D, and showed preliminary efficacy of niraparib and pembro combination for treatment of heavily pretreated TNBC or platinum-resistant OC. No significant overlapping toxicity was noted. A phase 2 study is currently enrolling. Supporting translational work funded by SU2C.

Clinical trial identification: NCT02657889

Legal entity responsible for the study: TESARO, Inc.

Funding: TESARO, Inc. and Merck and Co.

Disclosure: P.A. Konstantinopoulos: Consulting/Advisory: Merck, Vertex. J.C. Sachdev: Consulting/Advisory: Celgene Honoraria: Celgene. L. Schwartzberg: Consulting/Advisory: Eisai, Teva, Amgen, Bristol-Myers Squibb, Helsinn Therapeutis, Tesaro, Spectrum Pharmaceuticals Speakers' Bureau: Genentech, Bristol-Myers Squibb, Amgen. U.A. Matulonis: Consulting/Advisory: Merck KGaA, AstraZeneca, Immunogen, Tesaro, Genentech P. Sun, J.Y. Wang, W. Guo, B. Dezube: Employment: Tesaro Stock: Tesaro. D. Bobilev: Employment: Tesaro Stock: Tesaro Travel, Accommodations, Expenses: Tesaro G. Aktan: Employment: Merck Stock: Merck. V. Karantza: Employment: Merck Sharp & Dohme Stock: Merck Sharp & Dohme Patents, Royalties, IP: Merck Sharp & Dohme. S. Vinayak: Travel, Accommodations, Expenses: Tesaro.

1145PD Adoptive cell therapy with tumor-infiltrating lymphocytes for patients with metastatic ovarian cancer: A pilot study

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Background: Metastatic ovarian cancer (OC) is often diagnosed at an advanced stage and treated with standard platinum-based chemotherapy after which the majority of patients will experience recurrent/progressive disease with a poor prognosis. Adoptive cell therapy (ACT) with tumor-infiltrating lymphocytes (TIL) has shown impressive results in malignant melanoma, but has only been investigated scarcely in other cancers. This pilot study has tested TIL based ACT in patients with metastatic OC. Preliminary data has previously been presented at the European Society of Medical Oncology (ESMO), the Society of Immunotherapy of Cancer (SITC) and the Cancer Immunotherapy & Immunomonitoring (CITIM) conferences. In this abstract the final results of the study is presented.

Methods: Patients with platinum-resistant metastatic OC were treated with an infusion of TIL preceded by standard lymphodepleting chemotherapy (Cyclophosphamide 60 mg/kg for 2 days and Fludarabine 25 mg/m^2 for 5 days) and followed by stimulation with a continuous IL-2 infusion in accordance with the decrescendo regimen for up to 5 days. Stem cell harvest was performed before TIL therapy. Primarily, the feasibility and tolerability of the treatment was assessed. Secondarily, potential immune responses against tumor cells were monitored and objective response of the treatment was described.

Results: Only expected and manageable toxicities related to the treatment were observed. All patients had stable disease (SD) for a minimum of 3 months with 4 patients experiencing progressive disease (PD) at this time point. The last two patients had SD for 5 months. Modest antitumor reactivity was observed in expanded TIL, but not in peripheral blood lymphocytes (PBL) collected after treatment.

Conclusions: ACT with TIL in combination with decrescendo IL-2 is feasible and tolerable in patients with metastatic OC with only expected and manageable toxicities. Methods of altered TIL expansion or combining TIL therapy with checkpoint inhibitors in future studies could possible enhance the mainly transient clinical responses observed in this pilot study.

Clinical trial identification: NCT02482090

Legal entity responsible for the study: Center for Cancer Immune Therapy, Department of Hematology and Department of Oncology, Herlev and Gentofte Hospital 2730 Herlev, Denmark

Funding: Center for Cancer Immune Therapy, Herlev and Gentofte Hospital Department of Oncology, Herlev Hospital and Gentofte Hospital University of Copenhagen The Danish Cancer Society OvaCure

Disclosure: All authors have declared no conflicts of interest.

1146PD Adjuvant therapy with autologous dendritic cell (DC) vaccine based on cancer-testis antigens (CaTeVac) in melanoma patients

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Background: Interferon-alfa (IFN) is still a standard and most widely used adjuvant therapy for patients (Pts) with skin melanoma. Nevertheless, the efficacy of this approach is doubtful despite decades of clinical trials. CaTeVac is autologous DC, derived from peripheral mononuclear cells of the patient, loaded with lysate of allogenic melanoma cell lines with high expression of cancer-testis antigens. We compared cohort of Pts receiving adjuvant therapy with CaTeVac with a cohort of consecutive Pts in our center who received IFN in the adjuvant setting.

Methods: Pts with morphologically proven melanoma received CaTeVac or IFN. CaTeVac was injected subcutaneously in doses from 5 to 20*10^6 cells per cycle (C.) in the following regimen: C.1 – 14 days, C.2-4 – 21 days, C.5-14 – 30 days. After a year of the therapy Pts were allowed to receive additional cycles: C.15-18 (3 mo each) and C.19-20 (6 mo each). Each C. consisted from cyclophosphamide 300 mg injection on day 1 and CaTeVac injection on day 4. Pts in control group received IFN until progression, toxicity or at least 1 year of therapy whatever comes first. Both groups of patients were followed with the same clinical and laboratory methods and in the same time intervals.

Results: Ninety Pts treated from 2009 to 2016 were included in the study: 48 received CaTeVac, 42 – IFN (2-high doses of IFN, 36 – low doses of IFN, 4 – IFN with dose escalation from 3 MIU until maximum tolerated dose achieved). Median of follow-up was 23 mo. Patients with stage III and IV were presented more often in CaTeVac group (79,2% and 20,8%) when compared to IFN group (68% and 4%, respectively). Stage I-II patients composed 28% of IFN group, none were in CaTevac group; X^2 test for stage p = 0,001. Median time to progression in CaTeVac was 11,4 mo, for IFN group - 6,9 mo (p = 0,097). Two-year progression-free survival was 42% and 17% for CaTeVac and IFN, respectively. Relative risk for progression in 2 years was 0,74 (95% CI 0,57-0,96) for CaTeVac. Median of overall survival was 79,8 mo in IFN group and was not reached in CaTeVac group (p = 0,352) with plateau at 58% after 41 months.

Conclusions: Rather promising results received in our study justify performing of randomized trials with CaTeVac versus IFN in adjuvant setting for patients with melanoma.

Legal entity responsible for the study: N.N. Petrov Research Institute of Oncology

Funding: None

Disclosure: A. Novik, S. Protsenko: Lector for MSD, Bristol-Myers Squib, Roche, Novartis. All other authors have declared no conflicts of interest.

1147PD Germline determinants of immune related adverse events (irAEs) in melanoma immunotherapy response

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Background: Single line or combination immune checkpoint inhibition (ICI) therapies in metastatic melanoma have shown high response rates and durable survival. However, while at least 50% of patients show positive response to ICI treatments, ~60% of treated patients develop severe irAEs with high morbidity, substantially reducing treatment benefits. To date, no clinical or molecular indicators have been identified to predict irAEs.

Methods: Using data from our germline whole-exome sequencing scan of 69 anti-CTLA-4 (ipilimumab; IPI) treated patients, 30 with grade 3-5 irAEs and 39 with grade 0-2 irAEs, we assessed the association of exonic variants with irAEs by logistic regression analysis. Next, we cross-referenced the signification associations with irAEs against 1,140 risk variants previously found in GWAS on autoimmunity. Finally, pathway analyses of germline associations have been performed to identify biological networks involved in the susceptibility of IPI-related irAEs.

Results: We found most significant associations with increased risk of severe irAEs for two germline variants: rs504963 (OR = 2.57, p = 0.005697) in 3'UTR of FUT2, previously associated in GWAS with multiple autoimmune traits, including psoriasis, lupus,

rheumatoid arthritis and celiac disease; and rs1738074 (OR = 2.209, p = 0.02528) in TAGAP found in GWAS for association with celiac disease and multiple sclerosis. While additional variants were also identified as significant, pathway analyses have found enrichment of associated variants in chemotaxis biological processes (p = 0.04).

Conclusions: Our approach provides the first evidence that germline variants previously associated with autoimmune risk modulate the susceptibility to irAEs in patients treated by ICI. This includes associations with severe irAEs for FUT2, a protein involved in H-antigen production and linked with multiple autoimmune diseases. We have also found enrichment of variants associated with irAEs in chemotaxis processes, critically important in migration of dendritic cells upon treatment with anti-CTLA4 ICI. Upon validation in larger patient subsets, these findings suggest novel personalized biomarkers predictive of IPI-related toxicty, potentially extending to other ICI treatments.

Legal entity responsible for the study: Tomas Kirchhoff

Funding: None

Disclosure: J.S. Weber: Consulting for Bristol-Myers Squibb, Merck, AstraZeneca and Genetech. All other authors have declared no conflicts of interest.

1148P A phase I/II safety study of tisotumab vedotin (HuMax®-TF-ADC) in patients with solid tumors

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Background: Tisotumab vedotin (Tv) is an antibody-drug conjugate composed of a Tissue Factor (TF) specific human IgG1 monoclonal antibody conjugated to a microtubule disrupting agent Monomethyl Auristatin E (MMAE). Tv is being tested in an ongoing Ph I/II dose-escalation study (NCT02001623) in patients (pts) with locally advanced and/or metastatic solid tumors known to express TF. Preliminary data were presented at ASCO 2015, abstract #2570; here, we present the full data set from the dose-escalation part.

Methods: Key eligibility criteria include PS 0-1, normal organ function and no bleeding disorder or invasion of large vessels. Pts were treated with a classic 3 + 3 dose escalation regimen of Tv once every 3 weeks (q3Wk). The primary study objective was to assess tolerability of Tv. Safety was reported according to CTCAE 4.03. Responses were evaluated according to RECIST 1.1.

Results: Twenty-seven pts were enrolled across 8 dose cohorts (0.3-2.2 mg/kg). Demography: mean age 61 yrs (range 43-73); gender 9 males and 18 females; median number of prior lines of therapy 3 (range 1-14). Three dose-limiting toxicities (diabetes mellitus type II, mucositis and neutropenic fever, all Gr 3) were seen in 3 pts in the 2.2 mg/kg dose cohort. The most common AEs seen in $\geq$ 20%: epistaxis (48%), fatigue (48%), anemia (41%), alopecia (30%), constipation (30%), nausea (30%), pyrexia (30%), decreased appetite (26%), abdominal pain (22%) and diarrhea (22%). SAEs (all pts): 29 events in 15 pts (56%), 1 SCCHN pt in the 0.6 mg/kg cohort died from tumor related bleeding. AEs Gr $\geq$ 3: 19 pts (70%) experienced 41 events. Efficacy: 14 pts (52%) achieved SD or better; 1 cervical cancer pt dosed 1.2 mg/kg with 2 prior treatment lines before trial entry achieved and maintained PR during entire study period. After study period, the pt was transferred to named patient use.
Immunohistochemistry (IHC): Samples from 25 pts were evaluable. TF expression was present in 20 (80%) samples.

Conclusions: Tisotumab vedotin demonstrated a manageable toxicity profile. Recommended Ph II dose was identified as 2.0 mg/kg q3Wk. Biological activity included SD in 13 pts and 1 pt with prolonged PR (cervical cancer).TF was found widely expressed across investigated indications by IHC. Data warrant further exploration in solid tumors.

Clinical trial identification: NCT02001623, release date November 14, 2013

Legal entity responsible for the study: Genmab A/S

Funding: Genmab A/S

Disclosure: D.S. Hong: Research/Grant Funding: Bayer, Lilly, Genentech, LOXO, Pfizer, Amgen, Mirati, Ignyta, Merck, Daichi-Sanko, Eisai Travel, Accommodations, Expenses: MiRNA, LOXO Consulting Role: Bayer, Baxter, Guidepoint Global Other: Oncoreseponse (founder). R. Coleman: Member of Genmab's Advisory Board for Tisotumab vedotin. J. de Bono: Employee of The institute of Cancer Research, Served on Genmab Advisory Board, have served as advisor on advisory boards for multiple industry partners incl. AstraZeneca, Daiichi-Sankyo, Genentech, GSK, Merck, Pfizer, Sanofi, Taiho a.o. S. Lisby, L. Basse: Employee of Genmab and hold stocks in the company. All other authors have declared no conflicts of interest.

1148PD Immunotherapy in patients with concurrent solid organ transplant, HIV, and Hepatitis B and C

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Background: Anti PD-1/L1 (PD1) agents are being used to treat various tumor types. Most trials have excluded patients (pts) who have had a solid organ transplant (SOT), HIV, or Hepatitis (Hep) B and Hepatitis C. The safety and efficacy of PD1 in this setting is unknown.

Methods: Pts treated at 16 centres that had a transplant, HIV, Hep B/C were included. Patient demographics, tumour characteristics, toxicity, response and survival data, and the effect on the underlying condition were collected.

Results: 42 pts were identified; 29 with melanoma, 6 bladder carcinoma (BC), 2 hepatocellular carcinoma (HCC), 2 renal cell carcinoma (RCC), 2 mesothelioma (meso), and 1 each of gastric carcinoma, glioblastoma multiforme (GBM) and non-small cell lung cancer (NSCLC). 5 pts with SOT (4 renal,1 liver) had melanoma received pembrolizumab; 3 had progressive disease (PD), 1 partial response (PR), and the pt with liver transplant had graft rejection and died from this after 1 dose. 11 pts had HIV; 2 with detectable viral load. 8 pts had pembrolizumab (7 melanoma, 1 HCC), 2 nivolumab (1 melanoma, 1 RCC) and 1 atezolizumab (BC). No pt had loss in viral control or immune reconstitution inflammatory syndrome. 2 had complete response (CR), 1 PR, 4 stable disease (SD) and 4 PD. 14 pts had Hep C; 9 with detectable viral load, 6 on anti-viral therapy and 5 with cirrhosis. 6 received pembrolizumab (5 melanoma, 1 meso), 7 nivolumab (4 melanoma, 1 each of NSCLC, BC, RCC) and 1 atezolizumab (BC). No pt had loss in viral control, 1 developed grade 3 colitis but no one developed hepatitis. 2 had CR, 9 SD and 3 PD. 12 pts with Hep B; 8 with detectable viral load, 6 on anti-viral therapy and none with cirrhosis. 8 had pembrolizumab (5 melanoma, 1 each of GBM, gastric carcinoma and meso), 4 nivolumab (2 melanoma, 1 BC, 1 HCC). No pt had loss in viral control.1 had CR, 1 PR, 8 SD and 2 PD. None of Hep B or Hep C pts developed immune related hepatits.

Conclusions: Immunotherapy appears to have activity in patients with SOT, HIV and Hep B and Hep C. It can be given to renal transplant pts without rejection, however this is not universal . PD1 does not appear to adversely affect the viral control in HIV and Hep B and Hep C pts.

Legal entity responsible for the study: Human ethics approved protocol at Melanoma Institute Australia

Funding: None

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1149P Results of the randomized, placebo-controlled phase I/IIB trial of CV9104, an mRNA based cancer immunotherapy, in patients with metastatic castration-resistant prostate cancer (mCRPC)

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Background: CV9104 is a novel prostate cancer immunotherapy based on sequence-optimized, free and protamine-complexed mRNA encoding the antigens PSA, PSMA, PSCA, STEAP1, PAP and MUC1. Safety and immune responses to the predecessor therapy CV9103 encoding 4 of the antigens have been described previously. We assessed whether immunotherapy with CV9104 on top of standard of care (SOC) results in longer overall survival than placebo plus standard of care in patients with mCRPC.

Methods: After completion of a safety lead-in phase I, men with chemo-naïve, oligosymptomatic/asymptomatic mCRPC without visceral metastases were randomized 2:1 to intradermal CV9104 or placebo (P). Double-blinded treatment was continued beyond initial progression until progression under first subsequent SOC therapy or toxicity. The primary endpoint (EP) was overall survival (OS). Key secondary EPs included radiographic progression-free survival (rPFS1/rSPFS from randomization until initial progression/second progression on SOC therapy and rPFS2 from start of SOC therapy to second progression), time to symptom progression and cellular and humoral immune responses.

Results: 197 patients (pt) were randomized 2:1 to either CV9104 ($n = 134$) or P ($n = 63$). Pt characteristics, median number of administrations and first subsequent SOC therapies were well balanced between the arms. No significant difference in OS was found, median (m) OS was 35.5 months (mo) [28.-NE] in the CV9104 arm vs. 33.7 mo [28.7-NE] in the P arm (hazard ratio [HR] 1.1, 95% CI 0.70-1.76; one-sided $p = 0.33$). There were also no significant differences in the rPFS endpoints and time to symptom progression. Incidence of Grade $\geq$3 AEs (51.1% vs. 59.7%) and serious AEs (44.5% vs. 43.5%) was similar in both arms, injection site reactions and flu like symptoms were more frequent in the CV9104 arm.

Conclusions: CV9104 did not improve OS compared to placebo. Additional clinical outcomes and analyses of cellular and humoral immune responses will be presented and impact on further development will be discussed.

Clinical trial identification: EudraCT number: 2011-006314-14

Legal entity responsible for the study: CureVac AG

Funding: Study Sponsor: CureVac AG

Disclosure: A. Stenzl: Membership of advisory board CureVac. A. Heidenreich: Advisory board - Astellas, Bayer Healthcare, IPSEN, Jansen Honoraria - Amgen, Astellas, Bayer, Dendreon, Ferring, IPSEN, Jansen, Sanofi, Takeda Grants - AMGEN, Astellas, Sanofi. J. Loriot: Advisor for Sanofi, Astellas, Janssen, Roche, MSD, Astra Zeneca, BMS. Research grant: Sanofi. S.L. Perez Gracia: Research funding: Curevac. Advisory Boards: Curevac. S. Gillessen: Advisory Boards/IDMC (compensated): AAA International, Active Biotech AB IDMC, Astellas Pharma, Bayer, Bristol-Myers Squibb, Clovis, Curevac, Dendreon Corporation, Ferring, GlaxoSmithKline, Innocrin Pharmaceuticals, Janssen, Cilag, MaxiVAX SA, Millennium Pharmaceuticals, Novartis, Pfizer, 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): Amgen, Astellas Pharma, Bayer, Janssen, Sanofi Aventis Group. Patent: Pending patent application for a method for biomarker WO 2009138392 A1. U. Klinkhardt, V. Reus, S.D. Koch, H.S. Hong, T. Seibel, U. Gnad-Vogt: CureVaćs employee. A. Schroeder: Previous employee of CureVac AG, current employee of Merck KGaA. O. Schönborn-Kellenberger: Consultant of CureVac AG. K. Fizazi: Advisor for Amgen, Astellas, Bayer, Janssen, Takeda, Sanofi, Orion, Essa, Genentech, Astra Zeneca, Clovis. All other authors have declared no conflicts of interest.

1150P Phase II clinical trial of peptide vaccination for advanced head and neck cancer patients induced immune responses and prolonged OS

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Background: The peptides derived from ideal cancer-testis antigens, including LY6K, CDCA1 and IMP3 (identified using genome-wide cDNA microarray analyses), were utilized in immunotherapy for head and neck squamous cell cancer (HNSCC). In this trial, we analyzed the immune response to and safety and efficacy of vaccine therapy.

Methods: A total of 40 patients with advanced HNSCC were enrolled in this trial of peptide vaccine therapy, and the OS, PFS and immunological response were evaluated using enzyme-linked ImmunoSpot (ELISPOT) and pentamer assays. The peptides were subcutaneously administered weekly with IFA. The primary endpoints were evaluated based on differences between HLA-A*2402-positive (A24(+)) patients treated with peptide vaccine therapy and –negative (A24(-)) patients treated without peptide vaccine therapy among those with advanced HNSCC.

Results: Our cancer vaccine therapy was well tolerated. The OS of the A24(+)v accinated group ($n = 40$) was statistically significantly longer than that of the A24(-) group ($n = 18$) (MST 4.9 vs. 3.5 month, respectively, $p < 0.05$). One of the patients exhibited a complete response. In the A24(+) vaccinated group, the ELISPOT assay identified LY6K-, CDCA1- and IMP3-specific CTL responses in 85.7%, 64.3% and 42.9% of the patients, respectively. The patients showing LY6K- and CDCA1-specific CTL responses demonstrated a longer OS than those without CTL induction. Moreover, the patients exhibiting CTL induction for multiple peptides demonstrated better clinical responses.

Conclusions: The immune response induced by this peptides vaccine may improve the prognosis of patients with advanced HNSCC.

Legal entity responsible for the study: Yoshihiro Yoshitake

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1151P Phase I study of glypican-3-derived peptide vaccine therapy for patients with refractory pediatric solid tumors

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Background: The carcinoembryonic antigen glypican-3 (GPC3) is a good target of anticancer immunotherapy against pediatric solid tumors expressing GPC3. In this non-randomized, open-label, phase I clinical trial, we analyzed the safety and efficacy of GPC3-peptide vaccination in patients with pediatric solid tumors.

Methods: We conducted a phase I study of pediatric patients with solid tumors. GPC3 is a target of anticancer immunotherapy against some pediatric solid tumor especially hepatoblastoma. Vaccinations were carried out biweekly from the first until disease progression with the primary endpoint being the safety of GPC3-peptide vaccination and the secondary endpoints being immune response, as measured by interferon (IFN)-γ enzyme-linked immunospot assay and Dextramer staining, and the clinical outcomes of tumor response, progression free survival (PFS), and overall survival (OS).

Results: A total of 18 patients (7 hepatoblastoma, 4 rhabdomyosarcoma, 3 brain tumor, 1 MRT, 1 pancreatoblastoma,1 Wilms tumor, 1 germ cell tumor) were enrolled from 5 hospitals, all cases showed no dose-limiting toxicity (DLT), which was the primary endpoint of this trial. No grade 3-4 hematological and non-hematological toxicity due to GPC3 vaccine therapy occurred. Clinical benefit ratio was 66.7% with six long SD (SD during more than 24 weeks; 5 hepatoblastoma,1 MRT) The GPC3-peptide vaccine induced a GPC3-specific CTL response in seven patients, with PFS and OS significantly longer in patients with high GPC3-specific CTL frequencies than in those with low frequencies. Furthermore, we established GPC3-peptide-specific CTL clones from a resected-recurrent tumor from one patient, with these cells exhibiting GPC3-peptide-specific cytokine secretion.

Conclusions: GPC3 peptide vaccine therapy is well tolerated in heavily pretreated pediatric patients with refractory solid tumors especially hepatoblastoma with acceptable toxicities in outpatient setting and keep good QOL.

Legal entity responsible for the study: AKO hosono

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1152P Phase 1 study of HSP105-derived peptide vaccine for patients with advanced esophageal cancer/colo- rectal cancer

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Background: The HSP105 protein has been identified in pancreatic cancer by the SEREX method, and this protein has also been reported to play a role in controlling

apoptosis in cancer cells. HSP105 is highly expressed in various human cancers, including colorectal cancer, esophageal cancer, pharyngeal cancer, pancreatic cancer, breast cancer, and melanoma. We have therefore identified the respective HSP105-derived peptides that bind to HLA-A24 and HLA-A2(EP1536006, JP5112615, JP5291641, US9,404,925). We investigated the safety and efficacy of HSP105-derived peptide vaccine for patients ((pts)) with advanced esophageal cancer/colo-rectal cancer.

Methods: We conducted a multicenter phase 1 study of HSP105-derived peptide vaccine for pts with advanced esophageal cancer/colo- rectal cancer. The recommended dose is determined based on the incidence of dose-limiting toxicity (DLT) during phase 1a (P1a). Pts will then be added in phase 1b (P1b) to investigate the safety and efficacy of the vaccine. The vaccine was injected intradermally every 7 days. The primary objective of this study was to evaluate DLT (P1a), response rate (P1b). Progression-free survival, treatment failure rate, and toxicity were also evaluated as secondary objectives. As exploratory endpoint, immunological effect was investigated.

Results: A total 30 pts (HLA-24 group 15pts, HLA-02 group 15 pts) were enrolled and grouped into level 1 which received intradermally administration of peptide vaccine (emulsifying agent: Montanide ISA 51 VG) 3 mg/body. No DLT occurred and no major safety problems were reported throughout the trial. Although pts with objective clinical efficacy was not apparent, 7 pts showed stable disease 2 months after initiation of treatment. The HSP105-derived peptide vaccine induced HSP105-specific CTL response in 15 pts (50%) of 30 pts. Additionally, we established several HSP105 peptide-specific CTL clones from PBMCs and tumor of pts vaccinated with HSP105 peptide by single cell sorting using Dextramer or anti-CD107a antibody.

Conclusions: Although objective clinical efficacy was not apparent, HSP105-derived peptide vaccine appears safe and well tolerated with minimal local toxicity.

Clinical trial identification: Protocol number: UMIN000017809, Release date: Jun 22, 2015

Legal entity responsible for the study: National Cancer Center

Funding: 1. Health and Labor Science Research Grants for Research for Promotion of Cancer Control Programmes from the Ministry of Health, Labor and Welfare (2014). 2. Practical Research for Innovative Cancer Control from Japan Agency for Medical Research and development, AMED (2015, 2016).

Disclosure: All authors have declared no conflicts of interest.

1153P An observational clinical study with RAS peptide vaccine TG01 evaluating immune response, safety and overall survival in patients with non-resectable pancreatic cancer

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Background: The study evaluated the immune response, safety and survival of the TG01/GM-CSF vaccine, an antigen-specific cancer immunotherapy consisting of 7 RAS peptides targeted to KRAS mutated pancreatic adenocarcinoma, in treatment naive non-resectable pancreatic cancer patients (pts). TG01/GM-CSF was recently reported to elicit immune response and increased survival in resectable pancreatic pts (ASCO 2017).

Methods: 25 treatment naive non-resectable pancreatic cancer pts were immunised with TG01/GM-CSF at week 1, 2, 3, 4, 6, 10 (immunisation period) followed, after a 3 months pause, by a booster period of four weekly administrations. Pts were followed up for up to 12 months from 1st dose of TG01/GM-CSF. Immune response was evaluated by Delayed Type Hypersensitivity (DTH) skin reaction test, (S)AEs recorded throughout the study and survival data calculated using Kaplan-Meier.

Results: 14/25 pts (56%) had a positive DTH by week 10. The TG01/GM-CSF treatment was well tolerated with no reports of allergic or other adverse hypersensitivity reactions. 13 pts experienced 19 SAEs; 5 were due to disease progression, 13 were deaths due to disease progression, and one was treatment related (hypoglycaemia). Median survival (MS) from first administration of TG01/GM-CSF was for all treated pts (n = 25) 4.5 months, for DTH responders (n = 14) 5.1 months and for DTH non-responders (n = 11) 3.6 months. For the DTH responders the result compares favorably with untreated patients (MS ≈ 3.7 months)[1]. At 1 year, 4 pts of whom three DTH responders were alive. 1. Palmer KR *et al.*, Br J Surg: 81, 882-885 (1994).

Conclusions: In pts treated with TG01/GM-CSF monotherapy, immune response was recorded in 56% of the pts, results that correspond with data from a Phase I/II trial with a similar RAS peptide vaccine in non-resectable pancreatic pts[2]. Even though not statistically significant, the results indicate increased survival for the immune responders. In the otherwise incurable disease, the non-resectable pancreatic pts may therefore benefit from immunisation with TG01/GM-CSF RAS peptide vaccine with few side effects. 2. Gjertsen M *et al.*, Int J Can: 92, 441-450 (2001).

Clinical trial identification: Protocol CTN RAS 98010, 20.05.1998, Norway

Legal entity responsible for the study: Norsk Hydro ASA, Oslo, Norway

Funding: Norsk Hydro ASA, Oslo, Norway

Disclosure: J.A. Eriksen: Employed as chief technology innovation officer of Targovax ASA and hold stocks and options in the company. K. Risberg Handeland: Employee of Targovax ASA. All other authors have declared no conflicts of interest.

1154P Telomerase peptide vaccine combined with ipilimumab in metastatic melanoma: Reports from a phase I trial

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Background: The checkpoint inhibitor ipilimumab has improved survival for a proportion of patients with metastatic melanoma. However, most patients do not benefit from single agent immunotherapy. Patients lacking a spontaneous immune response may benefit from combining checkpoint blockade with a tumor-specific vaccine. UV1 is a therapeutic cancer vaccine consisting of three long synthetic peptides of the enzyme telomerase (hTERT). The UV1 peptides comprise epitopes recognized by T cells from cancer patients experiencing long-term survival following vaccination with a first-generation hTERT vaccine. The aim of this trial was to investigate the safety and efficacy of combining UV1 and ipilimumab in the treatment of patients with metastatic melanoma.

Methods: In a phase I, single center trial [EudraCT No. 2013-005582-39], patients with metastatic melanoma received treatment with UV1 (300 µg) + GM-CSF (75 µg) as adjuvant, combined with ipilimumab (3 mg/kg). Safety was assessed according to CTCAE v. 4.0, and tumor responses according to RECIST v.1.1. Immune responses against UV1 peptides were monitored in peripheral mononuclear blood cells by using 3H-thymidine proliferation and IFN-γ ELISPOT assays.

Results: 12 patients were recruited from Jan to Oct 2015. Treatment was generally well tolerated. Adverse events mainly included injection site reactions and diarrhea. Eleven serious adverse events (SAEs) were reported; nine treatment-related and two not related. Ten out of twelve patients showed an immune response (one negative, one not evaluable). Three patients obtained a partial response. Overall survival at 18 months was 75%. A comparison to a reference population from a phase IV ipilimumab trial in our center will be made.

Conclusions: Combining UV1 and ipilimumab is safe and induces clinical responses. The high proportion of immune responders and early induction of detectable immune responses suggest a synergistic effect due to *de novo* tumor-specific immune responses, likely due to blockage of CTLA-4, allowing expansion of hTERT-specific T-cell clones.

Clinical trial identification: EudraCT No. 2013-005582-39 Start date 16 Jan 2015

Legal entity responsible for the study: Ultimovacs AS Ullernschausséen 64 NO-0379 Oslo Norway Ultimovacs AS Ullernschausséen 64 NO-0379 Oslo Norway Ultimovacs AS Ullernschausséen 64 NO-0379 Oslo Norway Ultimovacs AS Ullernschausséen 64 NO-0379 Oslo Norway Ultimovacs AS

Funding: Ultimovacs AS

Disclosure: G. Gaudernack: Holder of a UV-1 vaccine patent, owns stock in Ultimovacs AS and is an employee in the same company. E.M. Inderberg: Inventor of the UV1 vaccine patent. W. Rasch: Holder owns stock in Ultimovacs AS and is an employee in the same company. J. Bjørheim: Employee at Ultimovacs AS. All other authors have declared no conflicts of interest.

1155P Results of an open label randomized phase II trial of CV9104, an mRNA-based multivalent cancer immunotherapy in patients (pts) with intermediate or high risk localized prostate cancer (PC) undergoing radical prostatectomy (RPE)

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Background: CV9104 is a multivalent mRNA-based active cancer immunotherapy containing sequence-optimized free and protamine complexed mRNA coding for six prostate cancer associated antigens (PSA, PSMA, PSCA, STEAP1, PAP and MUC1). CV9104 has been investigated in a placebo controlled Phase IIb study in pts with metastatic castrate-resistant PC. Administration of mRNA based immunotherapy by needle free jet devices has been shown to improve antigen expression and immunogenicity vs needle injection in preclinical models. The purpose of this study was to evaluate immune responses and safety of CV9104 administered by conventional intradermal (cID) injection or with a needle-free ID (nfID) injection device in pts with intermediate/high-risk localized PC.

Methods: 48 pts with intermediate or high risk localized PC and an indication to undergo RPE were randomized in a 1:1:1 ratio to receive presurgical CV9104 by nfID injection (960 µg mRNA per administration) (A), or cID injection (1920 µg mRNA per

administration) (B), or no treatment (C). CV9104 was administered in weeks 1, 2, 3 and 5 before RPE was performed in week 6-7. Postoperative CV9104 was offered to all pts with high-risk PC. Cellular (against all antigens) and humoral immune responders (against PSA, STEAP1, PAP, MUC1) were determined in blood at week 6-7 before RPE and 8 weeks after surgery. Further samples (prostatectomy, exprimate urine, serum) were collected for exploratory biomarker analyses.

Results: 48 pts were randomized (A: 15; B: 17; C: 16); Treatment with CV9104 was well tolerated using either nflD or clD injection. Most frequent adverse events (AEs) in Arms A and B were Grade 1-2 injection side reactions, transient flu-like symptoms (FLS) and AEs related to RPE. There were no CV9104 related Grade $\geq$3 AEs or SAEs. FLS were most frequent in Arm B (76.5%) vs Arm A (37.5%) and Arm C (6.3%).

Conclusions: CV9104 was well tolerated using either nflD or clD injection, with a safety profile similar to other previous mRNA-based cancer immunotherapies. Cellular and humoral immune responses including responses per antigen and additional biomarker results will be presented.

Clinical trial identification: EudraCT Number: 2013-004489-32

Legal entity responsible for the study: CureVac AG

Funding: Sponsor Clinical Trial: CureVac AG

Disclosure: M. Hipp, F. Doener, S.D. Koch, T. Seibel: CureVac employee. U. Klinkhardt, H.S. Hong, S. Brutlach, M. Fotin-Mleczek, U. Gnad-Vogt: CureVac employee. M. Scholl: previous CureVac employee. A. Schroeder: Previous CureVac employee; current employee Merck KGaA. O. Schönborn-Kellenberger: CureVac Consultant. All other authors have declared no conflicts of interest.

1156P Italian nivolumab expanded access programme: real-world results in non-squamous non-small cell lung cancer patients

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Background: Nivolumab monotherapy has shown survival benefit in patients (pts) with different tumors, including melanoma, lung cancer, renal cell carcinoma and head and neck cancer. The experience of pts and physicians in routine clinical practice is often different from that in a controlled clinical trial setting. Here, we report efficacy and safety of nivolumab monotherapy in pts with non-squamous non-small cell lung cancer (NSCLC) treated in the nivolumab Expanded Access Programme in Italy.

Methods: Nivolumab was available upon physician request for pts aged $\geq$18 years who had relapsed after a minimum of one prior systemic treatment for stage IIIB/stage IV non-Squamous NSCLC. Nivolumab 3 mg/kg was administered intravenously every 2 weeks to a maximum of 24 months. Pts included in the analysis had received at least 1 dose of nivolumab and were monitored for adverse events (AE) using Common Terminology Criteria for Adverse Events.

Results: In total, 1588 Italian pts participated in the EAP across 168 centers. Baseline characteristics of pts were representative of the population with non-squamous NSCLC, in the advanced disease setting. With a median follow-up of 7.8 months (1-21.9) and a median of 7 doses, the overall response rate (ORR) was 18%, including 10 pts (<1%) with complete response and 280 pts (17%) with partial response. Stable disease has been defined for 414 pts (26%) and totally 279 patients were treated beyond progression. As of March 2017, median overall survival (OS) was 11 months (range: 10.0-12.0). Response rates and survival were comparable among pts regardless age (< and $\geq$ 75 years), presence of brain metastasis and number of prior therapies. Overall, among 1588 pts, 1254 discontinued treatment for any reason, with only 80 pts (5%) who discontinued treatment due to related adverse events.

Conclusions: To date, this is the largest clinical experience with nivolumab in a real-world setting. These preliminary EAP data confirm that nivolumab seems to be an effective and safe therapy for pre-treated patients with non-squamous NCSLC, supporting its use in current clinical practice.

Clinical trial identification: CA209-966

Legal entity responsible for the study: Prof. Lucio Crinò

Funding: Bristol-Myers Squibb

Disclosure: F. Grossi: Consulting or Advisory Role: Bristol-Myers Squibb, Boehringer Ingelheim, Merck Sharp & Dohme, Pierre Fabre, AstraZeneca, Roche. F. De Marinis: Consulting or Advisory Role: Bristol-Myers Squibb, AstraZeneca, Roche. H.J. Soto Parra: Consulting or Advisory Role: Bristol-Myers Squibb, Lilly. F. Cappuzzo: Consulting or Advisory Role: Bristol-Myers Squibb, Pfizer, AstraZeneca, Roche. M. Tiseo: Consulting or Advisory Role: Bristol-Myers Squibb, Boehringer Ingelheim, Lilly, Merck Sharp & Dohme, Otsuka, Pierre Fabre, AstraZeneca, Novartis Pharma. M.R. Migliorino: Honoraria: Bristol-Myers Squibb, Boehringer Ingelheim, AstraZeneca Consulting or Advisory Role: Bristol-Myers Squibb, Boehringer Ingelheim, AstraZeneca. G. Tonini: Consulting or Advisory Role, Pierre Fabre, Molteni Farmaceutici, Novartis Pharma KK, Roche. F. Cognetti: Consulting or Advisory Role: AMtene Research Funding: Company: Genomic Health A. Scoppola: Travel, Accommodations, Expenses: IBSA. E. Cortesi: Honoraria: Janssen Corp Consulting or Advisory Role: Sirtex Medical. All other authors have declared no conflicts of interest.

1157P Correlation and differences in Effect sizes between Progression Free Survival (PFS) and Overall Survival (OS) among PD-1 inhibitors

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Background: Programmed death 1 (PD-1) inhibitors, such as nivolumab and pembrolizumab, have now been approved for various cancers based on results from pivotal randomized controlled trials (RCTs). These drugs are known for unconventional response patterns with varying effects on PFS and OS. We aimed to compare the correlation between PFS and OS and evaluate the differences in treatment size between PFS and OS for PD-1 inhibitors.

Methods: We carried out a systematic search on PubMed and conference abstracts for RCTs of nivolumab and pembrolizumab versus non-immunotherapy control and obtained data on median PFS, median OS for both arms and hazard ratio (HR) and confidence intervals (CIs) for PFS and OS. We evaluated the correlation between PFS and OS as well as between Delta (PFS) and Delta (OS). We also evaluated the ratio of HR of PFS to HR of OS for each trial (rHR) and obtained a summary rHR by random-effects meta-analysis across trials.

Results: Of 52 studies identified, a total of 11 phase 3 RCTs met the eligibility criteria. However, 2 trials didn't have data on OS. So our analysis includes 9 RCTs that had data on both PFS and OS (6 Nivolumab, 3 Pembrolizumab). There was no significant correlation between PFS and OS ($r = 0.676$, $R^2 = 0.457$, $P = 0.095$) or between Delta (PFS) and Delta (OS) ($r = 0.474$, $R^2 = 0.225$, $P = 0.282$). Using random-effects meta-analysis, treatment effects were in general 19% higher for OS than PFS (rHR 1.19, 95% CI 1.07 to 1.32, $p = 0.001$). There was no statistical evidence for lack of homogeneity ($I^2 = 0.0\%$, $p = 0.850$) and thus, subgroup analysis were not conducted. PFS and OS were discordant for 5 RCTs (3 Nivolumab, 2 Pembrolizumab) and in all these 5 RCTs, OS was significant but PFS was not. All RCTs ($n = 3$) showing benefit for PFS also showed benefit for OS. Only one RCT was negative for OS.

Conclusions: Unlike targeted therapies where benefit in PFS mayn't translate to OS, treatment effect sizes in RCTs of PD-1 inhibitors were greater for OS than PFS. The benefit in OS was poorly captured by PFS. There was no correlation between PFS and OS. OS should remain the standard endpoint for PD-1 inhibitor RCTs unless better surrogate endpoints such as immune-criteria based PFS are introduced and validated.

Legal entity responsible for the study: The authors

Funding: None

Disclosure: Y. Ando: Reports grants and personal fees from Taiho Pharmaceutical Co., Ltd., and personal fees from Merck Serono Co., Ltd., Ono Pharmaceutical Co., Ltd and Bristol-Myers Squibb. All other authors have declared no conflicts of interest.

1158P Is objective response rate (ORR) a valid primary endpoint in phase 2 trials (Ph2t) of immune checkpoint inhibitors (ICI) for advanced solid cancers?

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Background: ORR is commonly used as the primary endpoint in Ph2t. ICI have different mechanisms of action to chemotherapy or molecular targeted agents (MTA). The validity of ORR as a surrogate for progression-free survival (PFS) and overall survival (OS) with ICI is uncertain and may differ by tumor type. We performed a meta-analysis of randomized controlled trials (RCTs) in advanced solid cancers that compared ICI to chemotherapy, MTA or placebo to address this question.

Methods: We performed a literature search to determine the current Ph2t designs used in ICI trials. Efficacy data from single-arm trials and RCTs were extracted. Amongst the RCTs, correlations between ORR odds ratio (OR) with PFS hazard ratio (HR) and OS HR were examined for between randomized arms comparisons. Correlations within ICI treatment arms of the RCTs between ORR with PFS and OS rates were also studied. Using data from the RCTs, multivariable models that examined the relationships

between ORR, 6-month PFS and 12-month OS rates were developed and their predictive performances validated in the single-arm trials.

Results: Of 87 Ph2ts identified, most were single arm design (68%), and only 10% were RCTs with concurrent standard of care arms. ORR was the most common (60%) primary endpoint and PFS was uncommon (8%). A total of 20 RCTs (4 Ph2t and 16 phase 3 trials) with mature data were examined. There were 25 treatment comparisons in 8 different tumors (non-small cell lung cancer 44%, melanoma 24%). For RCTs in all tumors, the correlations (*r*) between ORR OR with PFS HR, ORR OR with OS HR, and PFS HR with OS HR were 0.63, 0.57 and 0.42 respectively. Within the ICI arms, *r* between ORR with 6-month PFS, ORR with 12-month OS, and 6-month PFS with 12-month OS were 0.37, 0.08 and 0.74 respectively. In the single-arm trials dataset, we were able to accurately predict 12-month OS using the actual 6-month PFS with the multivariate model developed from our RCTs dataset. Conversely, when ORR was used to predict 6-month PFS or 12-month OS, there was poor agreement between actual and predicted results.

Conclusions: These data do not support the use of ORR as a surrogate for OS in ICI trials. In future ICI Ph2t, 6-month PFS should be the primary endpoint rather than ORR.

Legal entity responsible for the study: Not applicable

Funding: None

Disclosure: M. Friedlander: Receives personal fees and grants with an advisory board position with AstraZeneca. Does not have any patents planned, pending or issued, broadly relevant to the work. All other authors have declared no conflicts of interest.

1159P Long term survival in patients responding to an Anti-PD-1/PD-L1 therapy and disease outcome upon treatment discontinuation

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Background: The long-term outcome of cancer patients responding to an anti-PD-1/PD-L1 immunotherapy (IT) remains unknown. This study aimed to describe the long-term survival of patients responding to anti-PD-1/PD-L1 monotherapy across multiple cancer types.

Methods: 306 patients treated with an anti-PD-1 or PD-L1 monotherapy in a phase 1 trial at Gustave Roussy were retrospectively analyzed over a period of 5 years. Major inclusion criteria were: at least 18 years-old, performance status 0-1, at least 1 infusion, evaluation by RECIST 1:1 and/or irRC. Multiple myeloma patients were excluded as they do not respond to anti-PD-1 monotherapy. All other cancer types (n = 19) were included.

Results: The overall objective response rate within this cohort of 262 patients was 29% (n = 76; 77% being evaluated by irRC). The median PFS of responders was 22 months and the median OS was not reached. The OS of patients responding to IT at 3 years was 76% and at 5 years was 63%. Long responders (patients with enough follow up to have tumor responses lasting more than 2 years) represented 11.8% of the cohort (31 patients). No death occurred in the 21 complete responders over this long term follow up. The median duration of response was not reached. Out of the 33 patients who disontinued immunotherapy, 9 patients showed a disease relapse (median response duration after treatment discontinuation: 6 months). Clinical and biological factors associated with response, long term survival, and secondary refractory disease will be reported at the ESMO meeting.

Conclusions: This study shows that, across cancer types, patients with objective tumor responses under anti-PD-1/PD-L1 immunotherapy have a high level of overall survival. Best survivals are seen with complete responses (no deaths in our cohort). Complete response rate might be a good short term surrogate marker for overall survival benefits. Clinical trials aiming at putting patients with partial responses under immunotherapy into complete responses should be assessed in a near future.

Legal entity responsible for the study: Gustave Roussy

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1160P Meta-Analysis of Anti-PD-1/PD-L1 Therapy Related Adverse Events in Clinical Trials

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Background: Anti-PD-1/PD-L1 immunotherapy is a major breakthrough in cancer treatment. With increasing use, its adverse event (AE) profile continues to be defined. We performed a meta-analysis to summarize AEs of anti-PD-1/PD-L1 therapy in clinical trials.

Methods: Clinical trials involving monotherapy with PD-1 or PD-L1 antibody in cancer patients published before April 1, 2017 were reviewed, and treatment related AE data were extracted. Meta-analysis of AE rates was done by Comprehensive Meta-Analysis (v2) using a random effects model. Average AE rate (Total AE No./Total Patient No.) was calculated in Microsoft Excel.

Results: 63 studies involving 10592 patients were included: 27 on nivolumab, 23 on pembrolizumab, 8 on atezolizumab, 4 on avelumab, and 1 on BMS-936559. Treatment related AE rates were summarized in the Table. In meta-analysis, all grade AE (AEx) rate was 71.5%, and grade 3-4 AE (AE3) rate was 14.9%. Common AEx included fatigue (>20%), pruritus, rash, diarrhea, nausea (10-20%), decreased appetite, arthralgia, vitiligo, pyrexia, hypothyroidism, and asthenia (5-10%). Most common AE3 included hyponatremia, lymphopenia, and fatigue (>1%). Average immune-mediated AEx/AE3 rates (%) were uveitis 0.9/0.0, pneumonitis 2.9/0.8, colitis 1.4/0.9, ALT increase 3.7/0.9, AST increase 4.0/0.8, pancreatitis 1.7/0.4, vitiligo 8.2/0.1, alopecia 1.0/0.0, asthenia 7.3/0.4, paresthesia 1.0/0.0, dysgeusia 2.2/0.0, peripheral neuropathy 1.5/0.0, hypothyroidism 7.0/0.1, hyperthyroidism 3.0/0.1, hypophysitis 0.5/0.4, and adrenal insufficiency 1.2/0.5. 31 (0.3%) treatment related deaths were reported. Pulmonary causes were most common, including 11 pneumonitis, 3 pneumonia and 1 respiratory failure.

Conclusions: Common AEs of anti-PD-1/PD-L1 therapy were primarily constitutional and gastrointestinal. Most grade 3-4 AE rates were < 1%. Rates of immune-related AE were low. Treatment related death was rare, and pneumonitis was the most common cause.

Legal entity responsible for the study: Yucai Wang

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1161P A standardized comparison of outcomes in patients (pts) with refractory, aggressive non-hodgkin Lymphoma (rNHL) from the SCHOLAR-1 analysis and the ZUMA-1 study of axicabtagene ciloleucel (axi-cel)

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Background: SCHOLAR-1 (Crump, ASCO 2016) is a large, pooled analysis of rNHL and demonstrated poor outcomes: objective response rate (ORR)= 26%; complete response (CR)=8%. ZUMA-1 is the first, multicenter trial of anti-CD19 CAR T cells (axi-cel) in rNHL and reported positive results: ORR= 82%; CR = 54%. This is a comparative analysis of outcomes from ZUMA-1 and SCHOLAR-1 after adjusting for imbalances in key covariates of patients enrolled.

Methods: Eligible pts for both studies had rNHL (stable disease ≤6 mos with ≥4 cycles frontline or ≥ 2 cycles later-line therapy, progressive disease as best response, or relapse ≤12 mos post autologous stem cell transplant). Standardized analyses were performed to account for other baseline covariates that were imbalanced between the studies despite similar inclusion criteria. These analyses equally weighted the proportions of patients with select prognostic covariates between the two studies. The pre-specified covariates selected for weighting were refractory subgroup and occurrence of SCT after refractory status. Sensitivity analyses included additional covariates.

Results: 101 ZUMA-1 pts received axi-cel; SCHOLAR-1 included data from 508 pts. Baseline characteristics for each study are listed in the Table. ZUMA-1 median follow-up was 8.7 mos. Using the standardized analysis, the estimated ORR and CR rates in SCHOLAR-1 were 20% and 6%, respectively. Standardized 6-mo survival rate for SCHOLAR-1 was 35%. Risk of death in ZUMA-1 was reduced by 77% relative to SCHOLAR-1 (P < .0001).

Table: 1161P

	ZUMA-1 mITT N = 101	SCHOLAR-1 Response N = 508
Age, ≥65 y, n (%)	24 (24)	74 (15)
Refractory subgroup, n (%)		
Primary refractory	2 (2)	101 (20)
Refractory to ≥ 2L	78 (77)	316 (62)
Relapse <12 mo post-ASCT	21 (21)	91 (18)
Received stem cell transplant*, n (%)	11 (11)	161 (32)
Prior lines of chemotherapy & ASCT	**n = 101**	**n = 417**
Median prior lines, n	3	2
ECOG performance score	**n = 101**	**n = 288**
0-1, n (%)	101 (100)	230 (80)
IPI Score	**n = 101**	**n = 215**
≥2, n (%)	74 (73)	142 (66)

*Autologous or allogeneic SCT at any time after determination of refractory status. ASCT, autologous stem cell transplant; ECOG, Eastern Cooperative Oncology Group; IPI, International Prognostic Index; mITT, modified intent-to-treat.

Conclusions: Despite the imbalances between the ZUMA-1 and SCHOLAR-1 studies, axi-cel appears to represent a significantly improved treatment option for pts with rNHL compared with currently available therapies as used in the SCHOLAR-1 study.

Clinical trial identification: NCT02348216

Legal entity responsible for the study: Kite Pharma

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1162P Predictive factors for poor progression-free survival in patients with non-small-cell lung cancer treated with nivolumab

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Background: Nivolumab (Nivo) has shown promising effects in patients with non-small-cell lung cancer (NSCLC) as a second- or later-line treatment. However, owing to the inclusion of random patients, the observed progression-free survival (PFS) in a clinical setting may be shorter than that in a clinical trial. For treatment effectiveness, it is important to clarify which patients may not experience any benefit from Nivo treatment. Therefore, in this multicenter retrospective study, we aimed to identify which patients would not be eligible for Nivo treatment.

Methods: In this study, data for 201 patients treated with Nivo during 17 December 2015 to 31 July 2016 at three respiratory medical centers in Japan were retrospectively reviewed. We collected clinical data including age, sex, smoking history, performance status (PS) score, body mass index (BMI), histological types, epidermal growth factor receptor (EGFR) mutation status, number of previous treatment, steroid use and laboratory data (Lactate Dehydrogenase (LDH) and C-reactive protein) at the time of Nivo treatment commencement. We investigated relationship between PFS and patient characteristics. Patients were followed-up for disease status until September 2016.

Results: The median age at the time of administration Nivo was 68 years, 135 patients were male, 157 patients had smoking history, 153 patients had a PS score of 0–1, and 23 patients received steroids. For all participants, median PFS was 2.9 months, over all response rate was 15.9% and disease control rate was 51.7%. In the univariate analysis, PS score ≥2, steroid use at baseline, and LDH level >240 IU/L was significantly associated with poor PFS. Furthermore, in the multivariate analysis, PS score ≥2 (hazard ratio [HR]: 1.57; 95% confidence interval (CI): 1.06–2.29; p = 0.027), steroid use at baseline (HR: 2.37; 95% CI: 1.44–3.74; p = 0.001) and LDH level >240 IU/L (HR: 1.63; 95% CI: 1.15–2.31; p = 0.007) were significantly associated with poor PFS.

Conclusions: PS score ≥2, steroid use at baseline, and high LDH levels were predictive of poor PFS in patients with NSCLC treated with Nivo. Careful monitoring is recommended for treating such patients with Nivo.

Legal entity responsible for the study: Fumio Imamura

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1163P Immunotherapy phase I trials in patients over 70 years with advanced solid tumours: The Gustave Roussy experience

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Background: More than half of new cases of cancer are diagnosed in patients over 65 years. However only few elderly patients have so far been included into trials, despite general awareness of the need. The revolution of immune checkpoint blocker development brings new hope in older patients because of clinical efficacy and low toxicity. Clinical indications are rising steadily but very few data are available in this population where co-morbidities, reduced functional reserve and immunosenescence may affect efficacy and tolerance.

Methods: All cases of patients enrolled in immunotherapy phase I trial between January 2012 and December 2016 in the Drug Development Department (DITEP) at Gustave Roussy were retrospectively reviewed. Case-control analysis was performed in a group of patients ≥ 70 years (elderly patients EP) matched to a group of patients < 70 years (younger patients YP) by trial and treatment dose. We compared cumulative incidence, grade and type of adverse events (AEs) and survival outcomes. Cumulative incidence was calculated according to Fine and Gray method and survivals using Kaplan-Meier method.

Results: Median age of EP and YP were respectively 75 (70 - 88) and 55 (22 - 70). Among the 46 EP and the 174 YP enrolled in 13 protocols, 10 (22%) and 23 (13%) patients experienced grade 3-4 AEs. Cumulative incidence of grade 1-2 AEs was significantly higher in EP versus YP (p < 0.05). For grade 1 AEs, median time of occurrence was 0.67 for EP *versus* 2.67 months for YP. For grade 2 AEs, median was not reached. No difference was observed between the two groups for grade 3-4 AEs (p = 0.50). Older age was not associated with lower dose intensity of treatment (p = 0.14). The response rate was respectively 14% for EP and 18.5% YP (p = 0.52). Median overall survival and median progression free survival were similar between the two groups (10.1 months, HR 0.93 [0.58-1.48] p = 0.77; 6.2 months, HR 1.41 [0.94-2.11] p = 0.09 for EP and YP, respectively).

Conclusions: Immune checkpoint blockade appears to be a practicable option of treatment for elderly patients. The toxicity and efficacy profiles appear similar to the ones in younger patients. Dedicated studies in this population are warranted.

Legal entity responsible for the study: Gustave Roussy

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1164P Patterns of progression under antiPD1/PDL1 in advanced NSCLC patients allow discriminating pseudo-progression from real progression

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Background: Immunotherapy (IT) is now a standard of care in advanced NSCLC patients. However, patients may present with various patterns of response, including initial progression followed by long stabilization or response, making it difficult to decide whether or not we should continue the treatment at the occurrence of progression. Our aim was to explore the patterns of responses based on CT-scans in order to differentiate real progression (PD) from pseudoprogression (PsPD).

Methods: We conducted a retrospective analysis of all NSCLC patients treated with IT in our Institution. All CT-scans were reviewed and the responses were assessed by RECIST 1.1 and iRECIST criteria. Seven different patterns of PD were considered based on the combination of target (T) and/or non-target (NT) and/or new lesions (NL). A confirmatory CT scan was performed at 4 weeks to discriminate real progression from PsPD. PsPD was defined as any decrease or stable disease for at least 6 months following an initial progression. Dissociated responses (DR) were defined as concomitant progressing and responding lesions for patients treated at least 6 months. Patterns of PD were correlated with overall survival (OS).

Results: Out of 202 patients treated by IT, 39 patients (19%) were excluded due to the absence of confirmatory CT. 87 patients (53%) had an initial PD, confirmed by a subsequent CT, or by death related to tumor progression. 14 patients (9%) experienced PsPD or DR. PsPD or DR patients had higher OS than PD patients ($p = <.05$). The pattern which was the most likely to confer PsPD or DR was the appearance of NL in the thoracic area (lung, pleura) or lymph nodes. The concomitant increase of T, NT and appearance of NL was only observed in real PD. New extra-thoracic visceral lesions (especially liver and brain) were very unlikely related to PsPD. New liver lesions occurring during IO were detrimental on OS ($p = <.05$).

Conclusions: On the first occurrence of progression upon IT, a concomitant increase of T, NT and appearance of NL or appearance of extra-thoracic visceral lesions were strongly suggestive of real PD. IT should be stopped in these patients, and a confirmatory CT scan should be avoided.

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1165P Immune checkpoint inhibitors following targeted therapies in MITF family translocation renal cell carcinomas

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Background: MITF translocation renal cell carcinoma (tRCC) is a rare RCC subtype harbouring TFE3/TFEB translocations with poor prognosis and no standard of care in metastatic setting. Program death ligand-1 (PDL-1) expression was reported in 90% of cases prompting us to analysed the benefit of immune checkpoint inhibitors (ICI) in this population.

Methods: A multicenter retrospective study was conducted to identify patients with MITF family tRCC who had received ICI in referral centres in France and USA. In the majority of cases, the diagnosis was confirmed by FISH. Overall response rate (ORR) according to RECIST criteria, progression-free survival (PFS) and overall survival (OS) were analyzed.

Results: Overall, 23 patients (4 males and 19 females) with metastatic disease were identified in 12 institutions (median age 33.5 years), all receiving ICIs as 2nd or later line. For first-line treatment, 19 (82.6%) patients received vascular endothelial growth factor receptor (VEGFR) inhibitors with a median PFS on therapy of 3 months (range, 1-22 months) and 2 (10.5%) responders. Regarding ICI, 19 patients received Nivolumab, 3 patients Ipilimumab and 4 patients combinations of ICIs +/- VEGFR inhibitors. Median PFS for patients under first ICI administered was 2.45 months (range, 1-40 months); among those, 4 patients experienced partial responses (17.4%) and 2 patients (9.5%) a stable disease with a median PFS of those responders under ICI of 9 months (range 8,3-30), similar to the first line PFS with VEGFR inhibitors [9 months, (range 1-22)]. One patient with partial response to Ipilimumab lasting for 9 months showed hyperprogressive disease following treatment by Nivolumab. With a median follow-up of 19 months, median OS was 23.5 months.

Conclusions: MITF family tRCC is an aggressive disease with occasional responses to ICI. Valid targets and clinical trials remain warranted in this disease.

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1166P Tumor flare reaction (TFR) in cancer treatments: a systematic review

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Background: In the last decade, TFR was described as a side-effect associated with immunomodulatory agents IMiDs (thalidomide and lenalidomide), and as a specific condition to chronic lymphocytic leukemia (CLL). However, this phenomenon is seen with the use of new immunotherapy (checkpoints inhibitors) in solid tumors, in addition, cases of TFR were reported in advanced gynecologic, prostate cancer and lymphoid malignancies. TFR is defined as an increase of lesion size related to treatment which simulates disease progression. This phenomenon that occurs after initiating cancer therapy is poorly understood and incidence is under-estimated, since not captured by Recist. It has been suggested that TFR may be the results of immune system activation and may precede tumor shrinkage. TFR is associated with morbidity, severe cases were reported, some of them life-threatening or leading to death. So, early recognition and initial management of patients presenting with TFR, is critical.

Methods: From 1985 to 2016, a search was performed in the Pubmed, ASCO and ASH abstracts to identify publications reporting TFR or pseudoprogression.

Results: The incidence of all grades of TFR in CLL, ranged from 28% in a study to 58% in another trial. In CLL, painful lymph nodes and/or spleen enlargement were reported with a sudden onset after the first dose. Following initial progression (TFR), tumor response in patients treated beyond progression, was reported in melanoma trials: 9.7% with ipilimumab, 10% with nivolumab, 6.7% and 12% with pembrolizumab, and in renal cell carcinoma 69% with nivolumab. Even if rare cases of life-threatening or fatal TFR were reported, symptoms are usually mild. While correct diagnosis and adequate management are critical, it is important to better recognize TFR, and avoid an effective treatment discontinuation. Some studies showed that treating patients beyond progression yielded tumor responses, considering TFR as predictive of response.

Conclusions: Treatment with immunomodulatory agents is associated with TFR. This is likely to be misinterpreted as progression, hence the need to identify appropriate clinical benefit criteria and the use of immune-related RECIST (irRC) in prospective trials for a better understanding.

Legal entity responsible for the study: Amina TALEB MD

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1167P Melanoma brain metastases patients treated with stereotactic radiosurgery and ipilimumab versus stereotactic radiosurgery alone: a systematic review with meta-analysis

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Background: The synergistic effects of radiotherapy and novel immunotherapy agents have shown renewed interest in cancer management. We examined survival outcomes in melanoma brain metastases (MBM) patients treated with stereotactic radiosurgery (SRS) and ipilimumab immunotherapy. We compared these outcomes with those of MBM patients receiving SRS without added immunotherapy.

Methods: We conducted the first systematic review with meta-analysis of studies comparing combined SRS and ipilimumab with SRS only in MBM. The protocol was published in the PROSPERO register for systematic reviews. MEDLINE and CENTRAL databases were searched using PRISMA method by three separate reviewers. Studies that examined SRS and ipilimumab compared to SRS without ipilimumab in MBM were included. Newcastle-Ottawa Scale Risk of Bias Assessment and the GRADE evidence quality rating method were used for qualitative appraisal. Statistical analysis was performed using Review Manager.

Results: We found 37 publications in our search and identified 4 retrospective studies to further assess; 3 studies were chosen for pooled-analysis. Evidence for survival benefits with combined treatment was rated "low", per GRADE method. Meta-analysis of 222 patients confirmed significant survival advantage for SRS and ipilimumab (pooled median survival: 16.8 vs. 6.2 months; HR 0.38, 95% CI: [0.28 – 0.52]; $p < 0.01$). One study's cohorts ($n = 58$) demonstrated non-significant trend for improved local and distant brain control. Otherwise, we found no differences in local control, distant brain control, radiation necrosis, or intracranial bleeding in our analysis.

Conclusions: Combining stereotactic radiosurgery and ipilimumab in melanoma brain metastases can dramatically improve survival rate compared to stereotactic radiosurgery without immunotherapy. There is no increased risk of radiation necrosis and/or intracranial bleeding with combining radiation and immunotherapy in this setting.

Legal entity responsible for the study: University of Central Florida College of Medicine

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1168P Estimation of benefice to anti-PD-(L)1 for metastatic patients by real-time quantitative and functional estimation of immune infiltrate with RNAseq

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Background: There is a current need to broadly evaluate the ability of RNA sequencing (RNAseq) to identify patients that will respond or not to PD-1 or PDL-1 immune checkpoint blockers (ICB) across metastatic tumor types.

Methods: RNA sequencing analysis were prospectively performed by a unique platform on patients' fresh frozen biopsies collected in the MOSCATO (NCT01566019) and MATCH-R (NCT02517892) prospective trials, ongoing at Gustave Roussy. We have analyzed more than 100 signatures related to immune cell types or immune mechanisms with several methods, and have evaluated their relation to PFS and OS under ICB, up to January 2017.

Results: RNAseq performed on a frozen tumor biopsy before receiving an ICB were available for 67 patients. The median time between the biopsy and start of the ICB was 41 days. The results of RNAseq analysis were available within a median of 42 days. The majority of patients were affected by either head-and-neck carcinomas ($N = 12$), bladder carcinomas ($N = 11$) or lung adenocarcinomas ($N = 11$). The majority of patients were treated with PD-1 ($N = 41$) or PD-L1 ($N = 28$) inhibitors either in monotherapy or in combination. The immune infiltrate was heterogeneous across patients and neither related to the histology nor to the location of the biopsy. The top RNAseq pipeline of analysis related to PFS were GSVA enrichment method and the combination of GSEA on Z transformed log TPM pipeline. Taken individually, 60% of the tested signatures had a significant relation to PFS under ICB whatever the pipeline used (logrank FDR<0.05). Using the best pipeline of analysis, the signatures with a significant continuous relation with PFS and OS were represented by 7 different T cells signatures, antigen processing and presentation, and PD-1 signaling (min-max ranges for PFS; HR 0.19-0.39, FDR = 0.0008-0.02 and for OS; HR = 0.17-0.32, FDR = 0.04 for all). An independent cohort is under constitution to validate these findings.

Conclusions: The use of RNAseq to orient patients to ICB is feasible. Estimation of immune infiltrate and function from RNAseq may be associated with treatment benefice either in term of PFS or in term of OS.

Clinical trial identification: MOSCATO (NCT01566019) and MATCH-R (NCT02517892)

Legal entity responsible for the study: Jean Charles Soria

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1169P Topography of Tumor Mutational Burden (TMB) and Immune-related Genomic Alterations (GA) Across Gastrointestinal Malignancies (GIm): A Study of 22,570 Cases

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Background: Response to immune checkpoint inhibitors (ICPIs) is mediated in part by tumor neoantigens. TMB has emerged as a predictive biomarker, but data is lacking in GIm. We examined TMB and concurrent GA across GIm to identify patient subsets for further study.

Methods: Comprehensive genomic profiling was used to determine TMB, microsatellite instability (MSI), and additional GA using previously described methods. GA were compared among anatomically defined tumor types and stratified by TMB status (mutations/DNA megabase), and those associated with response or resistance to ICPIs were compared to identify patient subsets.

Results: Median TMB was higher for tubular vs. non-tubular GIm ($p = 0.032$). Among the entire cohort, 3.5% and 7.4% of samples had a TMB >20 and >10, respectively. The proportion of tumors with TMB ≥10 was greatest within tubular foregut structures (esophagus, stomach, duodenum; 11.2%). MSI was observed across all anatomic subtypes (range: 0.2-6%). Overall 1.2% of cases harbored receptor tyrosine kinase (RTK) fusions; colon and biliary tumors with RTK fusions had high (11) and low (2.5) median TMB, respectively. Validated immunoresponsive GA including PD-L1 amplification and POLE mutations were mutually exclusive and enriched in tubular GI structures [esophagus (0.5%), stomach (0.8%), colon (0.9%), duodenum (1.3%) and rectum (0.9%)]. POLE mutation, but not PD-L1 amplification, correlated with high TMB (median 100 and 5.4, respectively). PIK3CA catalytic (H1047R) vs. helical (E545K) domain GA were strongly associated with high TMB ($p < 0.0001$), and similar findings were observed within MSI vs. MSS samples ($p < 0.0001$). Pre-existing GA that may decrease ICPI responsiveness including or JAK1 inactivating GA were rare (4.7% and 0.3% of cases, respectively). Representative clinical cases will be presented.

Conclusions: GAs associated with increased sensitivity and/or resistance to ICPIs are observed across GI cancers. Baseline genomic profling may inform rational patient selection for immunotherapy treatment. The observation that high TMB and MSI are strongly enriched for PIK3CA H1047R, and whereas low TMB and MSS are enriched for E545K, warrants further study.

Legal entity responsible for the study: Samuel J. Klempner

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1170P Analysis of POLE mutation and tumor mutational burden (TMB) across 80,853 tumors: Implications for immune checkpoint inhibitors (ICPIs)

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Background: Mutations of the DNA polymerase epsilon (POLE) can lead to a hypermutated tumor phenotype, in the absence of microsatellite instability (MSI).

Exceptional responses to ICPIs in POLE-mutated endometrial adenocarcinoma (EA), colorectal (CRC), and glioblastoma (GBM) are described, but detailed pan-tumor POLE analyses are lacking.

Methods: We prospectively analyzed 80,853 primarily advanced solid tumors using hybrid-capture based comprehensive genomic profiling. TMB (mutations/Mb) was calculated from 1.11 Mb of sequenced DNA (PMID: 28420421). Known genomic alterations (kGA) were defined as those reported as somatic in the COSMIC database or with published evidence indicating loss of function.

Results: POLE GA were identified in 5.0% of cases: melanoma (10%), duodenal adeno (DA, 7.8%), uterus carcinosarcoma (CS, 6.9%), EA (6.4%), unknown primary carcinoma (CUP, 6.3%), NSCLC (6.1%), CRC (5.1%), prostate adeno (5.0%), and GBM (4.6%). Most POLE GA were variants of unknown significance (VUS). POLE kGA were found in only 259 (0.3%) total cases, including ovary or uterus CS (2.2%), DA (1.3%), EA (1.2%), CRC (0.7%), GBM (0.6%), and CUP (0.6%). Patients with POLE kGA had a median age of 58 yrs (range 7-95); 53% were male. Median TMB in cases with POLE kGA, VUS and wild-type was 31, 9 and 3.6, respectively (each $p < 0.0001$). Of cases with POLE kGA, 54% had high TMB (>20), while 28% had low TMB (<5). The most common POLE kGA were R446Q (n = 77), P286R (n = 41), V411L (n = 29) and L424X (n = 17). R446Q, which is uncharacterized, was associated with low TMB ($p < 0.0001$) and predominantly germline, while P286R and V411L were associated with high TMB (each $p < 0.0001$), predominantly somatic, and enriched in CRC and EA. Inactivating GA in mismatch repair genes co-occurred with POLE kGA in 28% of cases; these cases had low MSI (7% vs. 5% for all kGA POLE cases), but very high TMB (median 230). PD-L1 IHC and outcomes will be presented for a subset of cases.

Conclusions: POLE GA are found across tumor types, but functionally significant GA may be less frequent than previously reported, particularly in advanced tumors. Identification of specific POLE GA associated with a hypermutated phenotype may be important to identify likely responders to ICPIs.

Legal entity responsible for the study: Foundation Medicine

Funding: Foundation Medicine

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1171P Checkpoint inhibitors in MSI tumors: Lessons from a monocentric experience

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Background: Microsatellite unstable (MSI) tumors have showed high response rates to checkpoint inhibitors. Nonetheless, patterns of response and characteristics of responders remain poorly understood. We hereby report preliminary results of response to immunotherapy in a cohort of patients (pts) with metastatic MSI tumors.

Methods: We included all pts with metastatic MSI tumors of various histologic types treated at our institute with checkpoint inhibitors as monotherapy or combinations. Somatic MSI status has been identified by immunohistochemistry with PCR at diagnosis and/or whole-exome sequencing in molecular screening trials at metastatic stage. Pts not previously known to have Lynch syndrome (LS) have been tested for inherited germline defect.

Results: From November 2014 through April 2017, 43 pts were enrolled. Main pts characteristics were as follow [median (range)]: age at treatment was 56.4 years (26-78) and number of previous treatment lines was 2 (1-5). The most frequently treated histologic types were gastro-intestinal (22/43: 15 colorectal (CRC), 2 small bowel, 2 biliary, 2 pancreatic, 1 duodenal) and gynecologic (11/43: 8 endometrial, 3 ovarian) tumors. Diagnosis of hereditary LS has been confirmed in 12 pts (28%) and screening results are awaited in 6 pts. After a median follow-up of 5.6 months and treatment with a median of 7 cycles (Range 1-47), median overall survival was not reached (NR) and median progression-free survival (PFS) was 11.1 months (95% CI 2.8-19.5). In the 38 evaluable pts who received more than 2 cycles, overall objective response (ORR) and stable disease rates were 31.6% (12/38; 4 complete responses (CR), 8 partial responses (PR)) and 18.4% (7/38) respectively. ORR was 33.3% (5/15; 4 CR, 1 PR) in CRC and 30.4% (7 PR/23) in non-CRC. PFS was significantly better in confirmed LS than sporadic tumors (NR and 5 months, respectively, $p = 0.028$) and in CRC than non-CRC (NR and 5.6 months, respectively, $p = 0.025$) in univariate analysis.

Conclusions: We reported high response rates and survival benefit with checkpoint inhibitors in pts with MSI tumors remarkably in CRC and LS. A comprehensive analysis of immune microenvironment would be of clinical interest to characterize responders and non-responders.

Legal entity responsible for the study: Gustave Roussy Cancer Campus

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Disclosure: All authors have declared no conflicts of interest.

1172P Single nucleotide polymorphisms in PD-L1 and outcome in nivolumab-treated advanced non-small-cell lung cancer patients

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Background: Nivolumab is an established agent in the management of non-small-cell lung cancer (NSCLC); however, while some patients with lung cancer have marked responses to nivolumab, others do not respond. To determine the efficacy of nivolumab, we retrospectively evaluated treatment response with respect to PD-1/PD-L1 SNPs among patients with NSCLC.

Methods: Between December 2015 and October 2016, a total of 68 patients with histologically or cytologically confirmed NSCLC were treated with nivolumab. Among these 68 patients, all of whom were registered at Kyoto University Hospital. Genomic DNA was extracted from peripheral blood and genotyping was performed using real-time PCR method. We investigated the possible correlation of PD-1/PD-L1 SNPs with PFS (progression-free survival) using Kaplan-Meier method.

Results: A total of 68 patients were evaluated for clinical response. The G allele of PD-L1 rs2282055 was significantly associated with better clinical response. The median PFS time was 4.2 months (95% confidence interval [CI], 1.7 months to 3.9 months) for the G/G and G/T genotypes of rs2282055 and 2.0 months (95% confidence interval [CI], 0.9 months to 2.2 months) for the T/T genotype ($P = 0.0388$). Moreover, the T/T and C/T genotypes of PD-L1 rs1411262 were significantly associated with better PFS in NSCLC patients treated with nivolumab.

Conclusions: The G/G and G/T genotypes of PD-L1 rs2282055 were significantly associated with better ORR and PFS in NSCLC patients treated with nivolumab. These results suggest that PD-L1 SNPs may be a biomarker for the efficacy of nivolumab.

Legal entity responsible for the study: Kyoto University

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1173P Efficient identification of neoantigens for personalized cancer immunotherapy in advanced refractory epithelial cancer patients

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Background: Recent genomic and bioinformatic technological advances have made it possible to dissect the immune response to personalized neoantigens encoded by tumor-specific mutations. However, rapid and efficient identification of neoantigens is still fraught with difficulty, and a systematic evaluation of personalized neoantigens based immunotherapy in advanced refractory epithelial tumors is lacking.

Methods: Tumor and ctDNA samples from 16 advanced epithelial cancer patients were underwent mutational profiling by cancer-associated genes panel. Neoantigens identification were performed by two strategies:(1) As classic mode, somatic mutations were subjected to in silico analysis to predict potential high-affinity epitopes and mutated peptides were denovo synthesized; (2) Hotspot mutations were matched to our customized driver mutation-derived neoantigens peptide library. Candidate neoepitopes were identified. Approximately 10^8 neoantigen loaded DC vaccine and 10^{10} bulk T cells composed of 10^9 neoantigen reactive CD8+T cells were generated for personlized immunotherapy.

Results: Among the sequenced patients, 1∼2 neoantigens recognized by autologous T cells have been successfully identified in 3 of 4 patients who utilized the classic mode and 6 of 12 patients who performed customized neoantigens library, respectively. Subsequently, a total number of 6 patients received immunotherapy targeting personalized neoantigen following immunomodulatory chemotherapy or radiotherapy. One patient with metastatic thymoma is achieving a complete and durable response beyond 12 months. In addition, immune related partial response was observed in another advanced pancreatic cancer patient. The remaining 4 patients achieved prolonged stabilization of disease with median PFS of 8.6 months.

Conclusions: Our costomized neoantigens library can provide a novel approach for neoantigens screening in advanced epithelial cancer patients. Besides, targeted sequencing is sufficient for somatic variant and neoantigen identification. The combination of two strategies can accelerate the neoantigen-based translational immunotherapy research into the paradigm of precision medicine.

Legal entity responsible for the study: Baorui Liu

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1174P KRAS mutations (KRAS-mut) and antiPD1/PDL1 therapy in a cohort of non-small cell lung cancer (NSCLC) patients (p): Experience from a single institution

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Background: AntiPD1/antiPDL1-based immunotherapy has changed dramatically the prognosis of NSCLC p with a substantial improvement of overall survival (OS) and even presenting long lasting responses in a subset of p. Several factors have been associated with the likelihood of better survival, which include the smoking exposure and the presence of KRAS-mut according to data from randomized clinical trials that compared chemotherapy to these immunotherapeutic agents.

Methods: By reviewing the clinical records of all stage IV NSCLC p treated with antiPD1/antiPDL1 agents, we identified p with KRAS-mut and evaluated their clinical outocomes.

Results: 129 p with advanced NSCLC were treated with nivolumab, pembrolizumab or atezolizumab (65.1%, 17.1% and 17.8%, respectively) from November 2013 to April 2017. 14 p were identified as adenocarcinomas with KRAS-mut (20.3%) of all non-squamous NSCLC (60p) once squamous cell carcinoma (39 p), p with Kras status unknown (15p), or due to other reasons (6p) were excluded. Kras-mut subgroup included 28.5% of female, with median age of 62.3 years, 92.8% of ever smokers, and PS0 and 1 in 21.4 and 78.6%, respectively. The immunotherapy consisted of nivolumab (71.4%) and pembrolizumab and atezolizumab (14.3% each) and was administered as 1st, 2nd and $\geq$3rd therapy in 7.1, 78.6 and 14.3% of p, respectively. 71.4% of p responded to therapy (64.3% were evaluated as partial response) and in 42.8% of p this response lasted $\geq$12 months (range 12-32). For this cohort of p median progression-free survival was 7.65 months and median OS was 58 months. At the time of analysis 57.1% were still receiving treatment.

Conclusions: Although the number of p is small, KRAS-mut p represent a subgroup of p that seem to substantially benefit from antiPD1/PDL1 agents in terms of both response and survival.

Legal entity responsible for the study: Medical Oncologya Department, Catalan Institute of Oncology Badalona

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Disclosure: All authors have declared no conflicts of interest.

1175P Comparability of programmed death-ligand 1 (PD-L1) expression on tumor-infiltrating immune cells (IC) and tumor cells (TC) in advanced urothelial bladder cancer (UBC) using clinically relevant immunohistochemistry (IHC) assays

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Background: PD-L1/PD-1 checkpoint inhibitors have shown clinical activity in UBC. It has been shown that PD-L1 expression on TC and/or IC correlates with clinical efficacy. In this study (ML39708) we examined technical comparability and inter-reader agreement of 4 clinically relevant assays for PD-L1 expression on IC and TC in locally advanced UBC.

Methods: Archived formalin-fixed paraffin-embedded sections from 30 patients with locally advanced UBC (70% cystectomies, 30% transurothelial resections) were selected from 150 cases based on PD-L1 status per VENTANA SP142 IC < 1%, 1–5% or > 5% (10 cases each). The study cohort was stained for PD-L1 using SP142, SP263 (VENTANA), 22C3, and 28-8 (DAKO) assays at two sites according to manufacturer protocols. Stainings were blinded and scored at 5 sites for the PD-L1 expression on IC (% per tumor area) and TC (%). All readers were trained on scoring IC with SP142.

Results: Percentage of IC cells staining for PD-L1 varied from 6.54 to 8.18%, and TC from 5.46 to 15.85%, depending on the assay used (Table). For each assay, IC staining varied slightly to moderately between readers, with small non-significant differences between assays. Results for TC were comparable except for significantly lower staining with SP142. Pairwise comparison revealed –0.3 to 1.6% differences in adjusted means between assays for IC, and for TC, –10.5 to –7.8% (SP142 vs other assays) and –1.9 to 2.7% (other comparisons). Retrospective allocation to binary cut-offs (1%, 5% and 10%) for IC or TC only predominantly showed substantial or high Kappa agreement scores (0.6–0.8) for IC and TC between assays for each reader.

Table: 1175P

Assay	PD-L1 on IC % (95% CI)*	Reader ICC†	PD-L1 on TC % (95% CI)*	Reader ICC†
VENTANA SP142	8.18 (7.32–9.03)	0.699	5.46 (2.85–8.07)	0.609
VENTANA SP263	7.08 (6.22–7.94)	0.729	15.85 (13.24–18.47)	0.805
DAKO 22C3	6.54 (5.68–7.39)	0.532	13.19 (10.57–15.80)	0.883
DAKO 28-8	6.88 (6.02–7.74)	0.573	15.15 (12.54–17.77)	0.845

*Adjusted means for each assay;
†Intra-class correlation per test between 5 readers

Conclusions: This is the first multicenter study for analytical comparison of PD-L1 IHC staining on IC and TC in UBC. High concordance rates across all assays were achieved between trained readers for scoring PD-L1 on IC and TC.

Clinical trial identification: ML39708

Legal entity responsible for the study: Roche Pharma AG

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1176P IDO-1 and PD-L1 predict response to immunotherapy in advanced non small cell lung cancer: An NGS and multiplex IHC analysis

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Background: PD1/PD-L1 inhibitors (IO) can be prescribed as first line treatment in high PD-L1 positive NSCLC pts. There is an important need for additional predictive factors to identify pts with PDL1 weak or negative NSCLC that could benefit from these.

Methods: In this retrospective study, pts with stage III/IV NSCLC eligible for an IO were selected. All pts consented for tissue analysis. Pt characteristics and outcome were collected. A NGS panel on 52 genes was performed with an immunochemistry analysis (PDL-1 with the SP-263 clone, CD8, PTEN, beta-catenine, MSI, FOXP3, IDO-1 and CD163). We used image analysis with density results. PD-L1 was classified as negative/weak/positive if 0/1-9%/10%+ of tumor cells were stained.

Results: Sixty-seven pts were enrolled. Median age was 64 years, 8 pts were never smokers, 90% had PS 0-1, 11.3%/58.1%/30.6% received an IO as 1st/2nd/3rd line or more, 69% had a non-squamous carcinoma. 38.7% of the tumors were PD-L1 positive, and 15% weak. Median progression-free survival (PFS) was 3.5 months (IC95%, 1.9-7.6), 12 months overall survival rate was 63.3% (IC 95% 46.6-76.1). The objective response rate (ORR) was 50.8%. In univariate analysis PS, line of IO, positivity for PD-L1 (cut

off 10%), CD8 (H-SCORE ≥ 284,4), FOXP3 (H-SCORE ≥ 155,4) and IDO-1 (H-SCORE ≥ 0,4) were significantly correlated with ORR and PFS. ORR was 77% in IDO-1 positive (n = 26), 32% in IDO-1 negative (n = 25) NSCLC pts. KRAS mutation, smoking status, histological type, response to platinum-based chemotherapy were not correlated with PFS and ORR. In multivariate analysis, positive PD-L1 and IDO-1 were the only factors correlated with ORR. ORR was 87.5% if both positive (n = 16), 60% if one of them was positive, 22.7% if both negative. Only IDO-1 was correlated with PFS.

Conclusions: Along with PD-L1, IDO-1 appears as a promising predictive factor for IO. A prospective validation is ongoing.

Legal entity responsible for the study: Sylvestre Le Moulec

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1177P Undiscovered immune heterogeneity in pancreatic adenocarcinoma (PDAC)

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Background: Our group previously identified three subtypes of human PDAC based on gene expression (PDAassigner, classical, quasi-mesenchymal (QM) and exocrine-like subtypes). Recently Bailey *et al.* published four subtypes that were concordant with our three subtypes except that their immunogenic subtype (enriched for immune genes) is a sub-subtype of the classical subtype. Here we applied our published prognostic/predictive colorectal cancer gene expression subtype classifier (CRCassigner) to PDAC patient samples to establish if these subtypes existed in PDAC and if they could be used to further refine our original PDAC subtypes.

Methods: CRCassigner signatures were used to classify 123 PDAC patient samples. Comparisons between different subtype classifications were performed using hypergeometric test. Patient survival analysis were performed using Kaplan-Meier plots and log-rank test. Pathway enrichment analysis was performed using gene set enrichment analysis (GSEA) on RNAseq expression profiles.

Results: We confirmed the existence of the five CRCassigner subtypes – enterocyte, goblet-like, inflammatory, stem-like and transit-amplifying (TA) - in PDAC. These subtypes were found to be sub-groups of original three PDAssigner subtypes. By combining our subtype classification with Bailey et al.'s we classified PDAC into six sub-subgroups of three published subtypes – classical (pancreatic progenitors and immunogenic); QM/squamous (stem-like and inflammatory) and exocrine-like/ADEX (TA and enterocyte). Interestingly, we observed differences in the distribution of immune cells between Bailey's immunogenic and our inflammatory subtypes. We noted a significant increase in the expression of most of the immune regulatory genes in the inflammatory (n = 7) subtype compared to the immunogenic subtype (n = 13).

Conclusions: This study further refines our published PDAC subtypes. The data reveals a new subgroups with a different immune and stromal profiles associated with different overall survival in this small data set. Further validation of these results is warranted to determine if subtype classifier can stratify patient samples for treatment with immunotherapy or immunotherapy combinations in PDAC.

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

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1178P Optimized protocols to determine PD-L1 expression on tumor tissue and cytology samples from non–small cell lung cancer (NSCLC) patients using the 22C3 antibody with various immunohistochemistry (IHC) autostainers

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Background: Pembrolizumab (pembro) is approved for treatment of PD-L1–expressing NSCLC in both treatment-naive patients with a PD-L1 expression tumor proportion score (TPS) ≥50% and previously treated patients with a PD-L1 TPS ≥1%. Testing for PD-L1 expression is mostly carried out using the PD-L1 IHC 22C3 pharmDx companion diagnostic test on the Dako Autostainer Link 48 (ASL48) platform. We developed optimized protocols for laboratory-developed tests (LDTs) that use the 22C3 antibody (Ab) concentrate on more widely available IHC autostainers for tumor tissue. We are also developing LDT protocols for cytology specimens.

Methods: PD-L1 expression was evaluated using the 22C3 Ab concentrate on 3 commercially available autostainers: ASL48, Ventana BenchMark ULTRA, and Leica BOND-III. Staining results were compared with the PD-L1 IHC 22C3 pharmDx kit on the ASL48 platform. PD-L1 expression was evaluated in tonsil specimens and a training set of 3 NSCLC specimens. Optimized protocols were validated in 120 NSCLC tumor tissue specimens. Cytology staining is being evaluated in 70 cell blocks from bronchial washes and pleural effusions with >100 tumor cells using the 22C3 Ab concentrate and optimized protocols.

Results: Protocols for LDTs were established on both BenchMark ULTRA and ASL48; the BOND-III autostainer protocol could not be optimized without a prohibitively high concentration of 22C3 Ab. Intraclass correlation coefficients, which measure the correlation of TPS score as a continuous variable, were 98.7% to 99.9% for the 22C3 Ab concentrate on the ASL48 and ULTRA platforms relative to the PD-L1 IHC 22C3 pharmDx kit on the ASL48. Interpathologist agreement was high for both LDTs and for the PD-L1 IHC 22C3 pharmDx kit. Optimized protocols for evaluation of PD-L1 expression in cytology specimens will also be presented.

Conclusions: Optimized protocols to determine PD-L1 expression in tumor tissue and cytology specimens using the 22C3 Ab concentrate on multiple autostainer platforms will expand the ability of laboratories to assess eligibility of patients with NSCLC for treatment with pembro in a reliable and reproducible manner.

Legal entity responsible for the study: Merck & Co., Inc., Kenilworth, New Jersey, USA

Funding: Merck & Co., Inc., Kenilworth, New Jersey, USA

Disclosure: S. Khambata-Ford: Employment with Merck; stock ownership with Bristol-Myers Squibb. L. Huang: Employment with Merck; stock ownership with Merck and GSK R. Mogg: Employment with Merck Sharpe and Dohme; stock ownership with Merck Sharpe and Dohme J. Juco: Employment with Merck & Co., Inc.; stock ownership with Merck, Illumina, and Regeneron All other authors have declared no conflicts of interest.

1179P Tumor-infiltrating lymphocytes expression in stage IIIc/IV of high-grade serous ovarian cancer: Variation with neoadjuvant chemotherapy and prognostic value

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Background: Ovarian cancer is a malignancy with a complex immune suppressive microenvironment mediated by the recruitment or induction of CD4+ regulatory T cell. The purpose of this study was to assess the effect of neoadjuvant chemotherapy (NACT) on immune activation in stage IIIc/IV of high-grade serous ovarian carcinoma (HGSOC), and its relationship to treatment response.

Methods: We retrospectively identified 33 patients diagnosed with HGSOC and treated with neoadjuvant platinum-paclitaxel from 2005-2014. Pre and post-neoadjuvant treatment tissue samples were submitted to *immunohistochemical* analyses with anti-CD3, CD4 and CD8 antibodies for the identification of tumor-infiltrating lymphocytes (TILs). Pathological response classification to NACT was made according to Steffen Bohm (JCO 2015). Response score system (CRS) was explicitly defined (CRS-1; No or minimal tumor response, CRS-2; Appreciable tumor response amid viable tumor that is readily identifiable, CRS-3; Complete or near-complete response).

Results: The average age of patients was 63.44 years (46.53-84.14). BRCA-mutation status was negative in 78.8% of patients (26/33); BRCA-mutation was positive in 6.1% (2/33); and variant of uncertain significance was found in 15.1% (5/33). The majority of patients (78.8%) were stage IIIc. The area under the ROC curve of post-surgery TILs for complete pathological response were: CD4 (epithelial): [0.73 (0.5; 0.97), p: 0.084]; CD4 (stromal): [0.74 (0.51; 0.97), p: 0.077] and CD8 (epithelial): [0.81 (0.63; 1.0), p: 0.02]. The expression of epithelial CD4 TILs in pre-surgery samples (≤ 0.5 [OR: 0.7(0.01; 0.86), p: 0.038]) and epithelial CD8 TILs in post-surgery samples (≤ 5.4 [OR: 0.1(0.01; 1.19, p: 0.06]) proved to be a marker of good prognosis for pathological response. Survival analysis demonstrated that the expression of epithelial CD3 ≤ 4.3 in pre-surgery samples is a marker of poor prognosis.

Conclusions: The high number of tumor-infiltrating lymphocytes in post-surgery samples was significantly associated with higher rates of complete pathological response and better prognosis. It is convenient to carry out further and multicentric studies to validate these results.

Legal entity responsible for the study: Hospital 12 de Octubre.

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Disclosure: All authors have declared no conflicts of interest.

1180P Development of OAT-1746, a novel arginase 1 and 2 inhibitor for cancer immunotherapy

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Background: Clinical success of PD-1/PD-L1 and CTLA-4 checkpoint inhibitors demonstrated that reactivation of anti-tumor immunity provides strong clinical benefits including curative responses. However, only a fraction of patients demonstrate long-lasting therapeutic effects prompting efforts to target additional pathways regulating antitumor immune response. Depletion of arginine inhibits proliferation and activation of T cells and is an important mechanism of immunosuppression. High plasma and tumor arginase (ARG) activity has been found in patients with a wide spectrum of cancers correlating with a poor prognosis. Therefore, we developed ARG inhibitors and report the immunoregulatory and antitumor activity of the lead compound (OAT-1746) alone or in combination.

Methods: The IC_{50} of the compounds was determined against the recombinant ARG1/2. M2-polarized, bone marrow derived murine macrophages and CHO cells transfected with human ARG1 were used to assess the cellular activity. Murine and human CD4+/CD8+ T cells were negatively isolated and incubated with anti-CD3/CD28 beads to trigger proliferation, CD3ζ levels were measured. The in vivo antitumor efficacy was evaluated in syngeneic mouse models after oral administration at 50 mg/kg bid.

Results: We have developed potent, selective, orally active inhibitors of ARG1 and 2. Our lead compound, OAT-1746, has a low nanomolar activity against ARG1/2 and < 50 nM cellular activity. It reversed the ARG1-inhibited proliferation of human and murine T cells and restored CD3ζ expression in ex vivo assays. In vivo, OAT-1746 showed good pharmacological properties with significant antitumor efficacy in multiple tumor models as a monotherapy and in combinations with checkpoint inhibitors and gemcitabine. The efficacy correlated with sustained PD effects: suppression of tumor arginase activity and 3-6 fold increase in plasma and tumor arginine concentrations that exceeded those required for the maximal stimulation of T cell proliferation. Induction of inflammatory markers in tumors confirmed reversal of immunosuppression. No toxicity was observed after multiple oral dosing in mono- or combinatorial therapies.

Conclusions: These results support the clinical development of OAT-1746 for cancer therapy.

Legal entity responsible for the study: OncoArendi Therapeutics SA

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1181P Pharmacokinetics (PK) and Pharmacodynamics (PD) of cergutuzumab amunaleukin (CA), a carcinoembryonic antigen (CEA)-targeted interleukin 2 variant (IL2v) with abolished binding to CD25

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Background: CA is a CEA-specific antibody fused to IL2v with abolished CD25 binding. Compared to wildtype (wt) IL-2, CA was designed to preferentially expand natural killer (NK) and CD8 T cells but not T regulatory cells (Tregs), to be retained within CEA+ tumors, and for improved PK.

Methods: In this FIH phase I study, PK/PD analyses were performed using samples from solid tumor patients treated weekly (QW) or biweekly (Q2W) with 6 – 40 mg CA monotherapy IV. Methods: PK - population modeling; PD analysis of baseline (BL) and on-treatment (OT) samples; flow cytometry of peripheral blood monocytes (PBMCs); immunohistochemistry (IHC) on tumor biopsies; PD-L1 expression using SP142 assay; measurement of plasma cytokines and sCD25.

Results: During cycle 1, CA exhibited prolonged exposure (8-fold) vs. wt IL2. Following multiple cycles, serum exposure showed typical target-mediated drug disposition kinetics, likely due to clearance by IL-2 receptor-expressing cells. In PBMCs from patients treated QW x 4, a significant increase in the absolute number of NK cells and CD8 T cells was seen (median of 13- and 2.3-fold, respectively). By contrast, moderate or no increase was seen in the absolute number of CD4 T or Tregs (median of 1.5- and 1.2-fold). Similar but less prominent changes were observed in patients treated Q2W. Treatment was accompanied by upregulation of the activation marker CD314 (NKG2D), which was undetectable on more than 20% of NK cells in 9 of 39 patients at BL, suggesting increased functional activity of NK cells in the affected patients. A transient increase in the level of various cytokines was seen, peaking 24 hours after administration. Changes in the level of sCD25 correlated with drug exposure. OT biopsies showed an increase in the number of infiltrating Ki67+ CD8 T cells and PD-L1+ immune cells (median of 3.5- and 3-fold, $n = 11$).

Conclusions: PK data confirmed that CA has longer exposure than wt IL2. PD data demonstrated preferential expansion and reinvigoration of NK and CD8+ T cells in both PBMCs and tumors. This data suggest that CA can be a potent combination partner for cancer immunotherapies targeting CEA+ solid tumors.

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

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Disclosure: I. Melero: Advisory board: Bristol-Myers, Roche-genentech, AstraZeneca, Lilly, Merck Serono, Bayer, Genmab, Alligator, Bioncotech, Tusk Grants from: Roche-Genetech, Bristol Myers, Bioncotech. J. Tabernero: Advisory boards for Amgen, Bayer, Boehringer Ingelheim, Celgene, Chugai, Genentech, Lilly, MSD, Merck Serono, Novartis, Pfizer, Roche, Sanofi, Symphogen, Taiho, and Takeda. V. Teichgräber: A permanent employee of F Hoffmann La Roche Ltd. With stock options L. Jukofsky: A Roche employee with stocks options. E. Rossmann: A permanent Roche employee with stocks options. G. Babitzki: A Roche employee. A. Patricia Silva: F.Hoffman-La Roche employee. M. Canamero: Roche employee with stock options. C. Boetsch: An employee of Roche with stock options. S. Evers: An employee and shareholder of Roche. J. Charo: The author is an employee and stockholder of Roche. All other authors have declared no conflicts of interest.

1182P A first-in-human study of a novel monoclonal antibody INCSHR01210 directed against programmed cell death protein 1 (PD-1) in patients with advanced or metastatic cancer

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Background: INCSHR01210 is a novel PD-1 inhibitor with a safety and activity profile that may be different from that of other PD-1 inhibitors.

Methods: This is an ongoing, open-label, Phase1, dose-escalation/tumor-expansion study to evaluate the safety of INCSHR01210 in patients (pts) with relapsed/refractory solid tumors (NCT02492789). In Part 1, INCSHR01210 was administered IV at 1, 3, 6, or 10 mg/kg, initially on Day 1 of a 28-day cycle (for safety, PK and PD) and then Q2W, in a standard 3 + 3 dose-escalation design. Based on Part 1 data, Part 2 consisted of different tumor expansion cohorts, in which fixed doses of INCSHR01210 (600 mg and 200 mg Q4W) were evaluated.

Results: As of data cutoff (3Feb2017), 23 pts were treated in Part 1 (median age, 62 y [range, 32–73]; 74% women). Treatment-related AEs in $\geq$ 20% of pts (all Gr; Gr3/4) were skin capillary hemangioma (61%; 0%) and diarrhea (26%; 4%). Skin capillary hemangiomas were scattered and typically: <1 cm in diameter; on the face and upper chest; considered Gr1/2; regressed after stopping INCSHR01210. Immune-related AEs were consistent with other PD-1 inhibitors and observed in 3 (13%) pts. Treatment discontinuation due to AEs was reported in 1 pt (10 mg/kg; Gr1 skin hemangioma [resolved after stopping treatment]). The PK profile showed a dose-dependent increase in half-life from 3 days at 1 mg/kg to 7 days at 10 mg/kg. The receptor occupancy (RO) assessment at 10 mg/kg showed a target PD-1 inhibition of ~80% for up to 28 days. Of 21 efficacy evaluable pts, 5 (24%) had PR (median DOR, 163 days [range, 36–316]) and 4 (19%) had SD. Pts with PR included 1 pt each with SCC of the parotid gland (1 mg/kg), breast cancer (1 mg/kg), RCC (6 mg/kg), bladder cancer (10 mg/kg) and ovarian cancer (10 mg/kg). Based on the safety (including tolerability of hemangioma), PK and RO data from Part 1 and from Part 2 at 600 mg Q4W flat dosing, the remainder of Part 2 patients were treated at the 200 mg Q4W flat dose; Part 2 data will be presented.

Conclusions: INCSHR01210 demonstrated manageable toxicity, but with Gr1/2 hemangioma not seen with prior PD-1 inhibitors. The recommended Phase 2 dose/schedule is 200 mg Q4W.

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Legal entity responsible for the study: Incyte Europe Sàrl, Geneva, Switzerland

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Employee: The University of Sydney, Westmead Hospital Corporate-sponsored research: Incyte. K. Woods: Corporate-sponsored research: CSL Ltd. All other authors have declared no conflicts of interest.

1183P Safety, efficacy, pharmacokinetics (PK) and pharmacodynamics (PD) of PF 06801591, an anti-PD1 antibody administered intravenously (IV) or subcutaneously (SC)

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Background: PF-06801591, a humanized IgG4 monoclonal antibody, blocks the Programmed Cell Death (PD-1) pathway by binding with high affinity to PD-1 and preventing its interaction with its ligands. A phase 1 study to assess the safety and tolerability of PF-06801591 after IV or SC administration is ongoing in patients (pts) with locally advanced or metastatic solid tumors.

Methods: PF-06801591 was administered at 0.5, 1, 3, or 10 mg/kg IV once every 3 weeks (q3w), or 300 mg SC once every 4 weeks (q4w). Dose escalation occurred after the first 2-4 pts at each dose cohort, with additional pts then enrolled to each cohort for further PD assessment. Safety, tolerability, PK, and PD were assessed for all pts.

Results: As of January 31, 2017, 26 pts (ovarian cancer, n = 12; sarcoma, n = 6; head and neck cancer [SCCHN]; n = 5; melanoma, n = 1; small cell lung cancer, n = 1; and malignant peritoneal neoplasm, n = 1) were treated in the dose-escalation phase: 0.5 (n = 2), 1 (n = 8), 3 (n = 7), 10 (n = 5) mg/kg IV, and 300 mg (n = 4) SC. Maximum tolerated dose was not reached. No drug-related SAEs or dose-limiting toxicities were observed. All drug-related AEs were Grade 1 or 2, and the most frequently reported in > 15% of pts include nausea (15.4%) and fatigue (15.4%). No dose-dependency of AEs was observed during IV dose escalation nor serious skin toxicity with SC administration. Four pts had partial response at 0.5, 1, and 10 mg/kg IV (ovarian pts) and 300 mg SC (SCCHN pt) and 3 pts had stable disease lasting >24 wks. There was a dose-dependent increase in the maximum concentration (C_{max}) and area under the concentration-time curve (AUC) after IV administration. Following SC administration, PF-06801591 was slowly absorbed, with a median time to C_{max} of 182 hours. The mean average concentration (C_{av}) after the first SC dose at 300 mg q4w was approximately 50% of the mean C_{av} following IV administration at 3 mg/kg q3w. Full receptor occupancy of PD-1 was seen in all dose cohorts.

Conclusions: Preliminary results demonstrate that PF-06801591 is well-tolerated with objective responses observed across the dose levels tested in both IV and SC forms. PK data confirmed the appropriateness of the dosing frequency.

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Legal entity responsible for the study: Pfizer Inc.

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1185P Safety, pharmacodynamic, and pharmacokinetic profile of TSR-042, an anti–PD–1 monoclonal antibody, in patients (pts) with advanced solid tumors

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Background: TSR-042, an immunoglobulin G4k humanized monoclonal antibody targeting programmed death (PD)–1, is being evaluated in a phase 1 study (NCT02715284) in pts with advanced solid tumors. We present preliminary safety, efficacy, receptor occupancy (RO), and pharmacokinetic (PK) data.

Methods: Pts were ≥18 years old with recurrent and advanced solid tumors, and adequate organ function. In part 1, pts received intravenous (IV) weight based doses of TSR-042 (1, 3, or 10 mg/kg every 2 weeks [Q2W]). Additionally, based on a PK predictive model from part 1, pts received 500 mg Q3W or 1000 mg Q6W TSR-042 IV in part 2A. Serum was collected for PK and RO analyses.

Results: 33 pts received TSR-042 in parts 1 (N = 21) and 2A (N = 12). No DLTs were observed. In part 1, all pts had ≥1 treatment-emergent adverse event (TEAE) with grade ≥3 TEAEs in 9/21 pts; most common TEAEs were fatigue (9 pts), nausea (7 pts), decreased appetite (6 pts), and dehydration (6 pts); 17/21 pts had treatment related TEAEs (TRTEAEs); 7/21 pts had serious TEAEs; 1 case of grade 3 TEAE (AST/ALT elevation) was deemed treatment related. In part 2A, 10/12 pts had ≥1 TEAE with grade ≥3 TEAEs in 1/12 pts; most common TEAEs were abdominal pain, fatigue, nausea, tachycardia and influenza like illness (each in 2 pts); 6/12 pts had TRTEAEs; no serious TEAE occurred. In part 1, 2 pts had a partial response (ovarian cancer [OC], small cell lung cancer) and 5 had stable disease (parotid gland, fallopian tube, anal canal, OC [2 pts]). Pts in part 2A have not yet been evaluated for clinical activity. TSR-042 PK was dose proportional for all dose groups in both parts. The mean trough serum concentrations were 40 (500 mg Q3W) and 50 mg/mL (1000 mg Q6W) after a single dose, which exceeds the 2.4 μg/mL required for ∼100% receptor occupancy in part 1.

Conclusions: TSR-042 is safe and well tolerated, with a safety profile expected for an agent targeting the PD-1 pathway, with evidence of linear PK and sustained target engagement at administration intervals up to 6 weeks. TSR-042 showed clinical benefit in heavily pretreated pts in the initial phase 1 study and will be further evaluated in defined tumor types in part 2B. Updated results will be presented.

Clinical trial identification: NCT02715284

Legal entity responsible for the study: TESARO, Inc.

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Disclosure: J.C. Sachdev: Consulting or Advisory: Celgene Honoraria: Celgene. A. Patnaik: Consult: Bayer Funding: Abbvie, Aeglea, Alexion, Amgen, Asana Biosciences, Ascentage, Astex, Calithera Biosciences, Forty Seven, Merck Sharp & Dohme, Plexxikon, Upsher-Smith, Novartis, Bayer, OncoMed, Jiangsu Hengrui Medicine. E. Im: Employment: TESARO Stock options: TESARO Travel, Accomodations, Expenses: TESARO. D. Jenkins: Employment: TESARO Stock: TESARO. K. McEachern, S. Lu, W. Guo, V. Kansra: Employment: TESARO Stock: TESARO. R. Tran: Employment: TESARO, Gilead Sciences Stock: TESARO, Gilead Sciences. V. Reichert, D. Bobilev: Employment: TESARO Stock: TESARO. G.J. Weiss: Employment: Cancer Treatment Centers of America Consulting/Advisory: Pharmatech, Paradigm, Blend Therapeutics Speakers' Bureau: Celgene, Pfizer, Quintiles, Amgen, Medscape Travel, Accommodations, Expenses: Cambridge Healthtech Institute. All other authors have declared no conflicts of interest.

1186P Phase Ia study of a humanized anti-PD-1 monoclonal antibody (JS001) in Chinese patients with refractory solid tumors

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Background: JS001, a recombinant humanized IgG4 antibody, selectively blocks the interactions of PD-1 with its ligands PD-L1 and PD-L2, and promotes host immune response against Cancer.

Methods: A Phase I open-label study is designed to evaluate the safety and tolerability of JS001 in solid tumor patients who are refractory to standard therapy. The study has a traditional 3 + 3 dose escalation design with planned cohorts at 0.3, 1.0, 3.0, 10 mg/kg Q2W and a fixed-dose 240 mg Q2W followed by a dose expansion.

Results: Enrollment was completed by October 2016 with 25 patients enrolled including 6 esophageal, 5 gastric, 6 nasopharyngeal, 2 pancreatic, 2 head and neck, and 1 Cholangio carcinoma and 3 melanomas. No dose limit toxicity was observed and no maximum tolerated dose was identified. Adverse events (AEs) occurred in 21/25 patients (84%), which were mostly grade 1/2, including fatigue (72%), elevation of liver enzymes (52%), proteinuria (40%), anemia (40%), rash (32%), fever (24%), hyponatremia (24%), hyper- or hypo-thyroidism (20%), and hypokalemia (20%). The emergence of AEs appeared unrelated to dose levels. JS001 PK analysis shows linear dose-dependent exposure with the elimination half-life of 6 to 15 days. Among 13 patients who had underwent at least one scheduled radiographic evaluation, 1 has confirmed complete response (melanoma), 2 have confirmed partial response (1 Head and neck and 1 esophageal), and 2 achieved stable disease. PD-L1 expression by IHC on pretreatment biopsy samples was correlated with the clinical response. Patients with positive PD-L1 staining (> 1%) observed a 30% response rate (n = 10, 1 CR and 2 PR) and a 50% DCR. Whole exon sequencing was performed on selected biopsy samples. Mutations on p53, MDM2, TAP2 et al, might contribute to the favorable response to immunotherapy. Interestingly, a divergent spectrum of mutations from mixed

response patients were observed on tumor cells from different metastases, which at the time of biopsy had drastically different clinical response to the treatment.

Conclusions: JS001 demonstrated an acceptable safety profile in solid tumor patients. Additional phase II studies to evaluate the safety and clinical activity of JS001 in selected tumor types are ongoing.

Clinical trial identification: Clinical Trial ID: NCT02857166

Legal entity responsible for the study: Sun Yat-sen University Cancer Center

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1187P A Phase 1/2 trial of intratumoral (i.t.) IMO-2125 (IMO) in combination with checkpoint inhibitors (CPI) in PD-(L)1-refractory melanoma

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Background: CPI have transformed melanoma treatment, however many patients remain refractory and subsequent treatment options are limited. IMO, a Toll-like receptor 9 agonist, may improve response to CPI by activating innate and adaptive immune responses to overcome immune escape. Initial clinical experience with IMO + ipi is promising (Uemera, ASCO-SITC 2017). Dose-finding is now complete and is the basis for this updated report.

Methods: Adults with unresectable or metastatic melanoma refractory to a PD-(L)1 inhibitor are eligible if they have tumor accessible to biopsy. IMO is administered i.t. to a single tumor at escalating doses during weeks 1,2,3,5,8, and 11 along with ipi or pem per the product label. The primary endpoint of Phase 1 is safety and for Phase 2 is overall response rate using a 2-stage design. Serial biopsies are obtained from both the injected and a non-injected lesion for immune analysis.

Results: A total of 22 subjects have been treated with either IMO-ipi (N = 18) or IMO-pem (N = 4) and dose-escalation is now complete for the IMO-ipi arm. Dose-limiting toxicities have not been reported. Immune-related AE were observed in 4 IMO-ipi subjects [hypophysitis (N = 2), hepatitis (1), colitis (1)]. These responded well to standard measures. Of 9 patients treated at the RP2D of 8mg, 6 have experienced clinical benefit (1CR, 1PR, 1uPR, 3 SD). Biopsies show maturation of the mDC1 subset ($CD1c^+CD303^-$), upregulation of PD-L1 by malignant cells, and an IFNα response gene signature. Biopsies of uninjected tumors show expression of $CD56^+$ and $Ki67^+$ effector $CD8^+$T cells in responding patients, indicative of an abscopal effect. Phase 2 accrual using the 8 mg IMO dose is ongoing.

Conclusions: IMO + ipi is a viable strategy to revive the immune response in CPI-resistant tumors and shows preliminary clinical activity worthy of further development.

Clinical trial identification: NCT02644967

Legal entity responsible for the study: Idera Pharmaceuticals

Funding: Idera Pharmaceuticals

Disclosure: J. Geib, S. Swann: Employment by Idera Pharmaceuticals. M. Cornfeld: Employment at Idera Pharmaceuticals. All other authors have declared no conflicts of interest.

1188P Clinical and immune effects patients with progressive disease treated with low dose of anti-CTLA-4, bortezomib, gemcitabine, naproxen and meloxicam

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Background: Several patients progressed with their cancer disease despite treatment and eventually they become refractory. We selected patients from several malignancies with PD despite standard of care treatment (n = 30) and performed a pilot clinical study to evaluate the effect of two intravenously, two oral and one subcutaneously agent. With this in mind and with a systematic review and immunomodulatory, anti-angiogenic and anti-tumoral validation of each drug was studied. We tested the preexisting CD8 and Th1 antigen specific immune response against several clinically relevant peptides from bad prognosis proteins.

Methods: 30 subjects were included after the CICS ethics committee approved the protocol. The inclusion criteria include ECOG=0, complete CT scan from neck, thorax, abdomen and pelvis, laboratory tests such as CBC, phase acute proteins, etc. The patients were accepted after initial IFN-gamma and Elispot assays were done to make sure we have only patients with Th1 and CD8 immune response, as we know that ipilimumab unleashes every T cell. The tumors included were PDAC (n = 5), HGSOC (n = 12), TNBC (n = 10) and MM (3). The patients received the oral and the IV treatment biweekly for 4 months.

Results: We had 60% of CR and 40% of PR. The tumor with more significant response was ovarian (90%). There was an immunological correlation of CD8 immune response between in both CR ($p = 0.001$) and PR ($p = 0.05$). The combination was well tolerated and after 16 months of stopping the treatment some patients have persistent CD8 antigen specific immune response.

Conclusions: The combination is clinically feasible, looks promising and we now understand the importance of preserving the immune response and the use of biomarkers to improve the rational and generate new combinations with this approach to improve clinical outcomes.

Legal entity responsible for the study: CENTRO DE INVESTIGACION DE CANCER EN SONORA CAMPUS CIUDAD OBREGON, SONORA, MEXICO

Funding: Fundacion del centro de investigacion de cancer en sonora (cics) campus ciudad obregon, sonora, Mexico.

Disclosure: All authors have declared no conflicts of interest.

1189P 4SC-202 plus anti-PD1: Breaking PD1-refractoriness to increase efficacy of checkpoint inhibition in patients with advanced melanoma

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Background: Despite successes in the treatment of melanoma patients with checkpoint inhibitors (CI), majority of patients do not respond to CI alone and a high unmet medical need remains for these patients. One promising approach is to enhance the immunogenicity and alter the tumor microenvironment from an immune-deserted to an inflamed phenotype with combination therapy. Epigenetic modulation has been reported as one key determining factor in shaping the immune microenvironment and compounds altering these processes (e.g. histone deacetylases (HDAC) inhibitors) are particularly promising.

Methods: Tumor bearing animals (CT26 & C38 syngenic models) were treated with 4SC-202, an oral clinical stage combined HDAC class I/LSD1 inhibitor, or CIs PD-(L)-1 alone and in combination. Tumor growth was assessed continuously and after approx. 2 weeks of treatment tumors were excised and analyzed by flow cytometry and gene expression profiling. Additionally, animals not intended for these analyses were further monitored and tumor growth/survival was monitored.

Results: 4SC-202 treatment led to an increase of MHC molecules and enhanced expression of inflammatory markers like IFN-γ and various chemokines in tumors. Detailed analysis of the tumors revealed that 4SC-202 strongly altered the immune cell composition; particularly the number of cytotoxic T cells (CTL) was markedly increased. Importantly, subsequent combination treatment of 4SC-202 with CIs in syngenic animal models showed a strong synergistic effect resulting in significant longer survival in both models leading to 55% of tumor free animals (C38 model).

Conclusions: In an upcoming study, patients with advanced melanoma who are refractory/non-responding to anti-PD-1 antibodies will be treated with 4SC-202 plus anti-PD1. These patients do not only represent a population with a high unmet medical need but melanoma also represents a model tumor for immunotherapy in general and CI in particular. We hypothesize that addition of 4SC-202 to anti-PD-1 antibody treatment may lead to increased immunogenicity of the tumor, an inflamed tumor microenvironment and ultimately to clinical benefit in anti-PD-1 refractory/non-responding advanced-stage melanoma patients.

Legal entity responsible for the study: 4SC AG

Funding: 4SC AG

Disclosure: F. Hermann: Employee of 4SC AG, Planegg-Martinsried, Germany.

1192P Cytomegalovirus reactivation in patients with refractory checkpoint inhibitor-induced colitis

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Background: Objectives: Immune checkpoint inhibitors have become a standard treatment in patients with metastatic malignant melanoma. Showing significant anti-tumor effects by unleashing the immune-system, checkpoint inhibitors can also cause high-grade immune-related adverse events, with immune-related diarrhea and colitis

(irColitis) being amongst the most frequent ones. While the majority of patients with irColitis respond well when treated according to standard treatment algorithms with corticosteroids +/- other immunomodulatory drugs such as infliximab, some patients do not show resolution of diarrhea and colitis. In the present study, we analyzed the frequency of therapy-refractory irColitis, the underlying cause and useful diagnostic measures.

Methods: In this retrospective, monocenter study we collected data of 370 patients with metastatic malignant melanoma. All patients had been treated with checkpoint inhibitors at the skin cancer unit of the Department of Dermatology at the University Hospital Essen from 2006-2016. Demographic and clinical data of all patients were collected. Digital patient records of all 370 patients were searched for the terms "diarrhea" and "colitis".

Results: We identified 41 patients with irColitis, the majority occurring during treatment with ipilimumab. Amongst these patients, 5 (12.2%) were refractory to standard immunomodulatory treatment with corticosteroids and infliximab. Therapy-refractory cases tended to show more severe inflammation in colonic biopsies performed during colonoscopy ($p = 0.04$). CMV-DNA in colonic biopsies and in plasma was significantly more often detectable in therapy-refractory cases (80% vs. 6.75% in non-refractory cases in biopsies, 80% vs. 0% in plasma). Presence of serum CMV IgM as well as positive immunohistochemical stainings of colon biopsies for CMV were also strongly associated with refractory colitis (40% in refractory vs. 0% in non-refractory cases), but not reliable markers in the majority of refractory patients.

Conclusions: This report on CMV reactivation during management of checkpoint inhibitor induced colitis emphasizes the need for repetitive diagnostic measures in treatment-refractory irColitis.

Legal entity responsible for the study: Ethics comittee of the University Hospital Essen, University of Diusburg-Essen

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1193P Pooled data analysis of the safety and tolerability of intravenous pelareorep in combination with chemotherapy in 500 + cancer patients

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Background: Oncolytic viruses are promising cancer immunotherapies but questions have been raised regarding their safety. Pelareorep (REOLYSIN, R), an unmodified Reovirus Dearing strain, selectively replicates and lyses cancer cells and induces anti-tumor immunity. To date, 900+ patients (pts) have been treated with intravenous (IV) pelareorep. In a phase 2 trial, its combination with paclitaxel improved overall survival (17.4m) vs paclitaxel (10.4m) in metastatic breast cancer (MBC) pts (HR 0.65, 80% CI 0.46-0.91, $p = 0.1$; Berstein et.al. AACR2017). A pooled analysis was thus conducted to better characterize pelareorep's safety profile in combinations with paclitaxel.

Methods: 1417 pts have been enrolled in 36 trials: 934 pts received IV pelareorep and 359 were in control arms. Data from 8 trials with paclitaxel (P), paclitaxel + pelareorep (PR), carboplatin + paclitaxel (CP) or carboplatin + paclitaxel + pelareorep (CPR) were pooled. Standard doses of P (weekly) and CP were administered. Pelareorep IV dose was 3x1010 TCID50 (5-6 doses q21-28 d). Various advanced solid tumors were evaluated, including the 81 pts with MBC.

Results: A total of 563 pts were included in P (86), PR (95), CP (118) or CPR (264) groups. Median age (59-62 y) and ECOG 0-1 status (90-96%) were similar across the groups. All pts in P or PR had received prior chemo but only 26% in CP and 38% in CPR. Fatigue was the most common grade $\geq$3 treatment related adverse event (TRAE) in PR (9.5%) and CPR (8.3%) vs P (8.1%) and CP (2.5%). Grade $\geq$3 neutrophil count decreased and/or WBC decreased were more frequent in PR (15.8%/17.9%) than in P (5.8%/3.5%), but addition of pelareorep did not increase the frequency or severity of other grade $\geq$3 TRAEs with P or CP. Serious TRAEs (%) of interest in P vs PR and CP vs. CPR, included: fever (0 vs 3.2 & 0 vs 3.8), febrile neutropenia (0 vs 1.1 & 3.4 vs 3.4), sepsis (1.2 vs 0 & 0 vs 1.5) and flu-like syndrome (0 vs 1.1 & 0 vs 0.8).

Conclusions: This is the largest database reported to date examining the safety of an IV viral agent. Pelareorep's administration, in combination with paclitaxel or carboplatin-paclitaxel, is safe and well tolerated. Continued evaluation in a registration trial is planned.

Clinical trial identification: NCI-US

NCI-GOG 0186H (NCT01199263). Ongoing, but not recruiting

NCI-8601 (NCT01280058). Ongoing, but not recruiting NCI- Canada (CCTG)

NCIC-CTG IND.213 (NCT01656538). Ongoing, but not recruiting Oncolytics Biotech Inc:

REO011 – UK (Karapanagiotou et al. CCR 2012) Completed

REO015 (NCT00753038) Completed

REO016 (NCT00861627) Completed

REO018 (NCT01166542). Completed

REO021 (NCT00998192) Completed

Legal entity responsible for the study: Studies were sponsored/conducted by NCI-US, NCI-Canada (CCTG) or Oncolytics Biotech Inc. See section of Clinical Trial Identification

Funding: NCI-US and NCI- Canada conducted their own studies and Oncolytics Biotech only provided the drug. Some studies were fully supported and conducted by Oncolytics. Details can be found in the Clinical Trial Identification section

Disclosure: A.A. Gutierrez: Chief Medical Officer and an employee of Oncolytics Biotech Inc. (or one of its affiliated corporations). Own shares in or have options to purchase shares in Oncolytics Biotech Inc. C. Reid: Paid consultant of Oncolytics Biotech. M. Crawford: Employee of Oncolytics Biotech Inc. (or one of its affiliated corporations) and own shares in or have options to purchase shares in Oncolytics Biotech Inc. K. Cheetham, A. Penman, N. Noronha: Employee of Oncolytics Biotech Inc. (or one of its affiliated corporations) and own shares in or have options to purchase shares in Oncolytics Biotech Inc. A. Dzugalo: Employee of Oncolytics Biotech Inc. (or one of its affiliated corporations) and own shares in or have options to purchase shares in Oncolytics Biotech Inc. M. Parsi, D. Galindez, R. O'Flynn: Paid consultant of Oncolytics Biotech. M. Coffey: President and CEO of Oncolytics Biotech Inc. As an employee of Oncolytics Biotech Inc. (or one of its affiliated corporations) he owns shares in or have options to purchase shares in Oncolytics Biotech Inc.

1194P Impact of prior immune checkpoint inhibitors on haematological toxicity in phase I patients receiving chemotherapy

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Background: Immune checkpoint inhibitors (ICI) are used increasingly and earlier to treat multiple cancers. Although rates of on-treatment myelotoxicity are low, there are no published data on the long-term effects of ICI. This is a pilot study to evaluate the impact of prior ICI exposure on chemotherapy-related myelotoxicity in patients in the Phase I setting.

Methods: We conducted a retrospective chart review of patients treated between 2012 and 2016 in the Drug Development Unit, The Royal Marsden Hospital. Multivariate logistic regression (including number of previous treatment lines and type of chemotherapy) was used to assess possible relationships between G3/4 neutropenia or thrombocytopenia and previous treatment with immunotherapy in patients receiving combination chemotherapy and targeted agents.

Results: We identified 99 patients (median age 62 years [range 34-79]; chemotherapy partners: cisplatin, carboplatin and paclitaxel). Fourteen patients (14%) received prior immunotherapy (PI) and 85 (86%) had no prior immunotherapy (NPI). Patient characteristics, including baseline full blood count, previous pelvic radiotherapy, sites of metastasis and serum albumin, were comparable between the 2 groups, apart from number of previous treatment lines, which was lower in the PI patients (median 1.5 vs 2, $p = 0.003$). The odds of G4 neutropenia were higher in the PI group (OR = 7.1, 95% CI = 1.7-29.6, $p = 0.007$). PI was associated with significantly increased odds of G3/4 thrombocytopenia (OR = 14.4, 95% CI = 2.7-77.4, $p = 0.002$) on chemotherapy. In multivariate analysis, incorporating lines of prior chemotherapy (OR 1.3, 95% CI = 1.0-1.5, $p = 0.037$) and type of chemotherapy (carboplatin vs others: OR 2.3, 95% CI = 0.9-6.2, $p = 0.094$), the odds of developing G3/4 myelotoxicity were significantly higher in PI patients (OR 4.3, 95% CI: 1.3-14.4, $p = 0.02$).

Conclusions: In our small cohort, previous treatment with immunotherapy was associated with the development of G3/4 myelotoxicity, especially thrombocytopenia, on subsequent chemotherapy. These preliminary data require further prospective validation but may impact on decision making regarding optimal sequencing of systemic therapy.

Legal entity responsible for the study: The Royal Marsden Hospital NHS Foundation Trust

Funding: None

Disclosure: J. de Bono: Consulting or advisory role: Astex, AstraZeneca, Genentech, Genmab, GSK, Merck, Pfizer, Sanofix Research Funding: AstraZeneca, Genentech, GSK, Sanofi, Janssen. U. Banerji: Receipt of grants/research supports: AstraZeneca, Chugai, Onyx, BTG Receipt of honoraria or consultation fees: Astex, Karus Therapeutics, Novartis, Vernalis. All other authors have declared no conflicts of interest.

1195P Compromised efficacy of PD-L1 blockade therapy in axenic (germ-free) mice with syngeneic tumors

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Background: The microbiome can have profound effects on the innate immune system. Since the innate immune system regulates the adaptive immune response to antigens, we hypothesized that the microbiome may influence anti-tumor responses to immune checkpoint inhibitors. Accordingly, we sought to characterize the anti-tumor

effects of PD-L1 blockade therapy between mice with syngeneic tumors in conventional (specific pathogen-free, SPF) and germ-free (GF) environments.

Methods: B16-OVA or Lewis Lung Cancer (LLC) cell lines were injected subcutaneously into the flanks of 10-12 week-old C57BL/6 mice in both SPF and germ-free (axenic) environments. Mice with B16-OVA tumors in SPF (n = 6) and GF (n = 12, 6 females and 6 males) environments, and mice with LLC tumors in GF (n = 6) environments were randomized to receive the murine PD-L1 blocking antibody 10B5 or an isotype control. Tumor growth was evaluated every 2-3 days until days 35-40 when all mice were euthanized. Tumor size was compared between treatment groups in each environment at day 24 with the Mann Whitney U test. This project was approved by Mayo Clinic's Institutional Review Board and Institutional Animal Care and Use Committee. Funding was provided by the NIH (K12 CA90628) and Mayo Clinic's Center for Individualizing Medicine's Microbiome Project.

Results: Whereas injection of the anti-PD-L1 antibody (clone 10B5) controlled tumor growth compared to treatment with an isotype control in SPF female mice with B16-OVA ($p = 0.05$), PD-L1 blockade had no effect on tumor growth in female axenic mice with B16-OVA ($p = 0.20$) or male axenic mice with B16-OVA ($p = 0.34$) or axenic mice with LLC ($p = 0.56$).

Conclusions: PD-L1 blockade therapy loses its anti-tumor efficacy in axenic mice. The microbiome may influence the efficacy of PD-L1 blockade through of its effects on both innate and adaptive immune responses to tumors.

Legal entity responsible for the study: Aaron Mansfield at Mayo Clinic

Funding: National Institutes of Health; Mayo Clinic's Center for Individualizing Medicine Microbiome Project

Disclosure: All authors have declared no conflicts of interest.

1197P iRGD enhances T cells infiltration and augments response to PD-1 gene knockout immunotherapy in gastric cancer

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Background: Poor infiltration of activated lymphocytes into tumors can be a fundamental factor limiting their efficacy and impeding the therapeutic effect of the checkpoint blockade immunotherapy. A tumor-penetrating peptide, iRGD, has a well-defined role in delivering drugs into extravascular tumor tissues in both the combination regimen and conjugated pattern, Here, we explored for the first time whether this cycled peptide could facilitate the infiltration of lymphocytes into tumor and furtherly overcome resistance to PD1 gene knockout immunotherapy.

Methods: We used polyethylene glycol-conjugated phospholipid (PEG-lipid) derivatives, a time-efficient and versatile platform, to immobilize iRGD on T cell membrane. The ability of iRGD modified or co-applied lymphocytes infiltration was detected in both the 3D tumor spheroids in vitro and subcutaneous tumor model and peritoneal tumor model of gastric cancer in vivo. Furthermore, the synergistic effect of iRGD modification and PD-1 gene knockout in adoptive T cell transfer immunotherapy was examined in a xenograft model of EBV-associated gastric cancer.

Results: In this study, we showed that T cells could be modified by the synthetic iRGD-PEG-lipid without compromising their vitality, expansion, phenotype and effector function. In vitro, co-administration of iRGD could promote the infiltration of T cells while iRGD modification made T cells spread more extensively throughout the multicellular spheroids. Near infrared results showed that iRGD modification made a tenfold improvement infiltration of T cells into tumors without a parallel increase in normal tissues. Most importantly, we demonstrated that iRGD modified T cells had superior antitumor efficiency owing to sufficiently increased T cells infiltration, and exhibited robust synergistic effect with PD-1 gene knockout immunotherapy.

Conclusions: Our study indicates that modification of T cell membrane with iRGD might be a potent strategy to increase T cells infiltration, thereby overcome the bottleneck of solid tumor immunotherapy.

Legal entity responsible for the study: Baorui Liu

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1198P Immunomodulation by regorafenib alone and in combination with anti PD1 antibody on murine models of colorectal cancer

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Background: Regorafenib is a small molecule inhibitor of multiple kinases involved in normal cellular functions and in pathologic processes such as oncogenesis, angiogenesis, and tumor immunity. Regorafenib is approved for the treatment of advanced colorectal cancer (CRC) and gastrointestinal stromal tumors. In addition, an overall survival benefit has recently been shown in patients with hepatocellular carcinoma who had previously progressed on sorafenib (RESORCE trial). Immuno-oncology treatment strategies have recently expanded the arsenal of highly effective cancer therapies. In addition to their activity in monotherapy, they are being tested in combination with other therapies, including those inhibiting angiogenesis, to further improve their antitumor activity. We investigated the immunomodulatory effect of regorafenib alone and in combination with a mouse-reactive anti PD1 antibody in mouse models of CRC.

Methods: CT26 or MC38 syngeneic tumors were treated with regorafenib alone and in combination with anti PD1. We monitored tumor growth and analyzed the immune status of tumors *ex vivo* at the end of the study. Immune infiltrates were characterized by flow cytometry, intratumoral cytokines by multiplex ELISA, and expression of immunologically relevant genes by qPCR.

Results: Both regorafenib and anti PD1 inhibited the growth of MC38 tumors vs control, and this effect was significantly enhanced by concomitant treatment or when regorafenib was given after anti PD1. Regorafenib treatment most consistently reduced tumor-infiltrating macrophages in both MC38 and CT26 tumors in a dose-dependent manner. Additionally, signs of M1-type macrophage conversion were detected by elevated inducible NO synthase and reduced arginase expression. This may be due to a regorafenib-mediated inhibition of the CSF1 receptor, as shown *in vitro* in the murine macrophage cell line RAW264.7. Anti PD1 treatment was associated with elevated interferon-g levels, indicative of enhanced T cell activation.

Conclusions: These results warrant further exploration of a combination of regorafenib and PD1 for the treatment of colorectal cancer.

Legal entity responsible for the study: Bayer AG

Funding: Bayer AG

Disclosure: S. Hoff, S. Grünewald, L. Röse, D. Zopf: Employees of Bayer AG, and some are shareholders of Bayer AG stocks.

1199P Effect of MEK inhibition on PD-L1 and MCH-1 expression and on cytokines production profile in NSCLC cells and in human lymphocites

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Background: Understanding of cancer-immune system interaction led to development of immunotherapy; anti-programmed cell death protein-1 (PD-1)/programmed cell death ligand-1 (PD-L1) antibodies are now used in non small cell lung cancer (NSCLC) treatment. MAPK cascade is a key intracellular network for tumor proliferation and recent data suggest that it is implicated in interplay of tumor and T-CD8+ cytotoxic lymphocytes (CTL).

Methods: We evaluated PD-L1 mRNA level by Real Time qPCR (RT-qPCR) and its protein production, togheter with MAPK proteins, by western blot (WB), in NSCLC cell lines. Then, we studied the changes in PD-L1 and major histocompatibility complex class-I (MHC-I) expression and cytokines' production, after MAPK-inhibition or -stimulation, by MEK-inhibitor, cobimetinib, or phorbol 12-myristate 13-acetate (PMA), respectively. In addition, we explored the effect of cobimetinib on cytokines' genes by RT-qPCR on cDNA, obtained from retro-transcription of RNA extracted from T-lymphocytes, derived from Peripheral blood mononuclear cells (PBMC) of healthy volunteers, by density gradient separation, and activated with anti-CD3/anti-CD28 coated beads.

Results: WB and RT-qPCR for PD-L1 in NSCLC cells revealed a consistent correlation between mRNA and protein levels, togheter with activated MAPK and MEK1/2 signals, and suggested that ectopic PD-L1 mainly depends on trascriptional regulation. PDL-1 levels were significantly decreased by cobimetinib and increased by PMA, suggesting that MAPK can regulate PD-L1. Moreover, MEK-inhibition resulted on cancer cells in increased synthesis of MHC-I, IFN-gamma, IL-6, IL-1B, and TNFalpha, involved in CTL activation, and on activated human pheripheral T-lymphocytes in increment of mRNA levels of IL-12, TNFalpha and IFNgamma, that are pro-inflammatory cytokines typical of CTL subset, that seems more involved in immune response against cancer.

Conclusions: These results demonstrate that MEK-inhibion induces the establishment of a pro-inflammatory microenvironment and may represent a potential mechanism to convert otherwise resistant cancers through treatment combination strategies of MEK-inhibitors and anti-PD-L1/PD-1 antibodies in NSCLC.

Legal entity responsible for the study: AOU Università della Campania "Luigi Vanvitelli"

Funding: AIRC

Disclosure: All authors have declared no conflicts of interest.

1200P Exploring personalized immunotherapy opportunities in colorectal cancer

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Background: Adoptive T cell therapy (ACT) with tumor-infiltrating lymphocytes (TIL) can induce prolonged clinical responses in selected patients with gastrointestinal tumors while a significant fraction of patients do not respond. The association between immune profiles and antigenic specificity of TIL and clinical responses remains unclear. We addressed these issues, including the recognition of neoantigens, in order to explore the potential of personalized cell-based and vaccine therapy in colorectal cancer (CRC).

Methods: Tumor specimens of primary (n = 11) and metastatic (n = 12) colon adenocarcinoma were dissected in fragments and cultured with IL-2 (6000U/ml) for 17-28 days. TIL were analyzed by multiparametric flow cytometric analyses and interrogated with private sets of predicted neoepitopes derived from non-synonymous mutations. T-cell responses against neoepitopes were detected by IFNγ ELISpot and validated with peptide-MHC multimers.

Results: TIL (i.e.>$50x10^6$ cells, mean±SEM 239±$52x10^6$) were obtained from 7 and 8 patients with primary and metastatic colon adenocarcinoma, respectively. In primary tumors, the highest potential for TIL expansion was observed for microsatellite-instable tumors as opposed to microsatellite-stable (MSS) tumors (mean±SEM 435±$194x10^6$ vs. 84±$34x10^6$ cells; p = 0.05, Mann-U). TIL yield was similar in primary and metastatic tumors, however in metastatic tumors the CD4/CD8 T cells ratio was higher (median 11 vs. 1; p = 0.002, Mann-U) and inversely correlated with TIL expansion (r_s -0.8; p = 0.005). Most (>90%) T cells had a phenotype of effector-memory ($CCR7^-CD45RA^-$) activated ($HLADR^+PD1^+TIM3^+$) cells. Mutational load (ranging from 23 to 2760) and potential neoepitopes (from 25 to 2373) were determined and, of interest, initial screening experiments identified 2% of neoantigen specific-TIL (mutMALT1; V380A) in a representative MSS metastatic tumor harboring only 47 missense mutations.

Conclusions: We demonstrate the spectrum of TIL expansion across CRC subtypes and stages, including the validation of neoepitopes in a non-hypermutated advanced tumor. These observations stress the potential of CRC patients for different strategies of personalized immunotherapy.

Legal entity responsible for the study: Centre de Thérapies Expérimentales. Département d'oncologie. Centre Hospitalier Universitaire Vaudois

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Disclosure: All authors have declared no conflicts of interest.

1203P Functional screening of B7H6-based chimeric antigen receptor (CAR) designs

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Background: B7H6, a stress-induced ligand for the NK-activating receptor Nkp30, is widely expressed at the surface of transformed cells yet absent in healthy tissues. This makes B7H6 an attractive target for a CAR T-cell therapy with broad clinical applicability, including colon cancer and neuroblastoma. CARs are artificial receptors comprising an extracellular antigen-binding region (often a single chain variable fragment (scFv)) fused to an intracellular T-cell activation tail (usually CD3ζ in tandem with one or two costimulatory domain(s)). Here, we report the *in vitro* screening of various B7H6-based CAR designs differing by either the origin of their targeting moiety (murine versus humanized scFv), the costimulatory signaling module (either CD28 or 4-1BB as a 2nd generation CAR) or a combination of CD28 and 4-1BB in a 3rd generation CAR context.

Methods: Primary human T-cell populations expressing the diverse B7H6-specific CAR constructs were compared for viability and fold expansion at the end of manufacturing as well as *in vitro* functionality (IFNg secretion and cytolytic activity when challenged with B7H6 expressing cell lines).

Results: All B7H6-based CAR T-cells yielded comparable fold expansion with high viability suggesting that the CAR design has no impact on process parameters. CARs with targeting moiety of murine scFv origin were functionally superior to humanized versions in terms of killing and IFNg release potentially due to a difference in target affinity between the scFv. Second generation CARs containing CD28 endowed CAR T-cells possessed superior *in vitro* anti-tumor activity compared to all other constructs. Cryopreservation of these 2nd generation CAR T-cells did not significantly reduce viability and potency post-thawing.

Conclusions: In these studies, a B7H6-based CAR comprised of murine scFv fused to CD28-CD3ζ signaling tail represented the best choice candidate after *in vitro* testing warranting further investigation. Subsequent studies will include *in vivo* xenograft models of colon cancer and neuroblastoma as well as target profiling through immunohistochemistry assessing B7H6 expression in a wide panel of tumor and normal tissues. This work focuses upon developing a package to support the clinical testing of B7H6 targeted CAR T-cell therapy.

Legal entity responsible for the study: Celyad sa

Funding: Celyad sa

Disclosure: B. Demoulin, L. Springuel, D. Daro, J. Bolsée, J. Houssa, F. Huberty, C. Jacques-Hespel, C. Marchand, J. Marijsse, T.L.T. Nguyen, N. Ramelot, B. Violle, C. Lonez, D.E. Gilham, V. Steenwinckel: Employee at Celyad.

1204P Concurrent immuno-radiotherapy in lung and renal cancer- a new treatment paradigm

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Background: Concurrent administration of checkpoint inhibitors and radiotherapy (Immuno-RT) remains investigational and is the subject of multiple clinical trials. Nivolumab is an anti-programmed death-1 receptor monoclonal antibody that exhibits checkpoint-mediated immune response against tumor cells. Nivolumab has received regulatory approval for the second-line management of metastatic non-small cell lung cancer (NSCLC) & renal cell carcinoma (RCC). Ionising radiation could increase the diversity & quantity of tumoral antigen presentation, thereby augmenting anti-tumour immune response achieved with checkpoint inhibitors. The aim of this study was to assess the efficacy & toxicity of concurrent administration of nivolumab and radiotherapy.

Methods: We identified 6 patients that received concurrent nivolumab and radiotherapy to 19 lesions; metastatic NSCLC (n = 4), metastatic RCC (n = 2). Treatment-related toxicities were identified by retrospective review of patient notes. Measurable lesions were assessed by RECIST 1.1 criteria. Pain score was used to assess symptomatic responses.

Results: Stereotactic and conformal radiotherapy were delivered to 9 and 10 lesions, respectively. Treatment sites (number of lesions): lung (n = 8), hip (n = 3), brain (n = 4), shoulder, scalp, ethmoid and adrenal. The gap between radiotherapy & nivolumab did not exceed 2 weeks for all patients. No grade 3-4 toxicities were observed. Two of the lung cancer patients developed grade 1 pneumonitis. Fractionation schedules included 48Gy/4 fractions (#), 40Gy/4#, 34Gy/4#, 22Gy/1#, 30Gy/10#, 25Gy/5#, 20Gy/4# and 20Gy/5#. Of the 14 measurable lesions, 86% had excellent response including complete response of 3 lesions. Symptomatic benefit was observed in 4 out of 6 treatment sites (66%).

Conclusions: The of role of concurrent nivolumab & radiotherapy in patients with metastatic NSCLC and RCC has never been reported previously. In our study, concurrent administration of nivolumab and radiotherapy appears to be well tolerated with excellent radiological and symptomatic responses. Ongoing clinical trials may help determine the future role of Immuno-RT in the rapidly evolving treatment paradigm of metastatic NSCLC and RCC management.

Legal entity responsible for the study: Jawaher Ansari

Funding: None

Disclosure: J. Ansari: Paid honoraria for lectures and/or advisory boards for Amjen, AstraZeneca, Pfizer, Novartis, Boehringer Ingleheim, Bristol-Myers Squibb, Roche and Sanofi. A. Shaukat: lecture fees and advisory board for Bristol-Myers Squibb. A. Alhamad: Advisory board for Bristol-Myers Squibb. All other authors have declared no conflicts of interest.

1205P Optimum fractionation of radiation dose to combine anti-PD-1 mAb in MC38 mice model

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Background: The irradiated tumor cell death can enhance antitumor immunity by inducing antigen expression on tumor cells and activating lymphocytes. Radiotherapy (RT) combined with immunotherapy has revealed promising outcomes in various animal models. However, the optimum fractionation of radiation for priming immune response is controversial. This study aimed to explore the fractionation of radiation to maximize immunity in combinatorial treatment.

Methods: Mice bearing MC38 murine colon cancer were treated with up to 24Gy radiation given in various sized fractions as 24Gy x 1f, 8Gy x 3f, 8Gy x 1f followed by 2Gy x 8f and 2Gy x 12f, and tumor growth followed. The immune response in the tumor, drainage lymph node(dLN) and spleen at 48h after radiation were assessed. 8Gy x 3f was chosen to combine anti-PD-1 immunotherapy. The abscopal effects and immune response were assessed by flow cytometry and immunohistochemistry(IHC).

Results: Single dose of 24Gy and 8Gy x 3f brought best tumor control. No abscopal effects was observed after radiotherapy alone. Fractionation of 8Gy x 3f increased the irradiated tumor infiltrating lymphocytes(TILs). However, conventional 2Gy doses decreased $CD4^+$TILs and $CD8^+$TILs and increased myeloid myeloid-derived suppressor cell (MDSC) in spleen significantly. As the optimal fractionation to maximize immunity, 8Gy x 3f was chosen to combine anti-PD-1 mAb. Compared to radiotherapy or anti-PD-1 mAb alone, 8Gy x 3f combining with anti-PD-1 mAb brought obvious abscopal effect. $CD8^+$T cells in the dLNs of the irradiated tumors were increased significantly in the combining group. Also, the combining treatment regimen increased $CD4^+$T cells and $CD8^+$T cells and decreased MDSC in the spleen. No serious toxicity of heart, liver, spleen, lung and kidney in each group was observed by using IHC.

Conclusions: Hypofractionation of 8Gy x 3f was the fractionation of radiation dose to maximize immunity, compared to single dose of 24Gy and conventional 2Gy doses. Radiation with 8Gy x 3f combining with anti-PD-1 mAb had synergistic antitumor effect.

Legal entity responsible for the study: Jinming Yu

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1206P Efficacy of tumor treating fields (TTFields) and anti-PD-1 in non-small-cell lung cancer (NSCLC) preclinical models

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Background: Tumor Treating Fields (TTFields) are an effective anti-neoplastic treatment modality delivered via non-invasive application of low intensity, intermediate frequency, alternating electric fields. TTFields is approved for the treatment of both newly diagnosed and recurrent glioblastoma. TTFields interrupt mitosis in cancer cells by disrupting microtubules and septin filaments, which play key roles in mitosis. The mitotic effects of TTFields include abnormal chromosome segregation that trigger different forms of cell death. We evaluated TTFields' effect on immunogenic cell death and its efficacy when combined with an immune checkpoint inhibitor (αPD1) in NSCLC.

Methods: Murine Lewis lung carcinoma (LLC) cells were treated with TTFields using the inovitro™ system. Levels of cell surface calreticulin (CRT) and intracellular ATP levels were evaluated using flow cytometry. High mobility group box 1 (HMGB1) secretion was measured using an ELISA assay. Mice inoculated with LLC cells were treated with isotype control, TTFields, αPD-1, or TTFields + αPD-1. Tumor volume monitoring and intra-tumor immune cell profiling were performed.

Results: TTFields induced elevated cell surface expression of CRT, decreased ATP levels, and promoted HMGB1 secretion. In vivo, the combined treatment of TTFields + α-PD-1 led to a significant decrease in lung tumor volume compared to all three other groups ($P < 0.001$). Significant increase in CD45+ tumor infiltrating cells was observed in the TTFields + αPD-1-treated mice. Infiltrating cells demonstrated a significant upregulation of surface PD-L1 expression. Both F4/80+CD11b+ cells and CD11c+ cells exhibited higher tumor infiltration and elevated PD-L1 expression, as compared to the control group. These findings indicate enhanced inflammatory antitumor environment conferred by the combination of TTFields + αPD-1.

Conclusions: Our results demonstrate that TTFields treatment potentiates immunogenic cell death in NSCLC cancer cells. Combining TTFields with specific immunotherapies such as anti-PD-1 may enhance antitumor immunity and result in increased tumor control. A phase III clinical study on TTFields in combination with either PD-1 inhibitors or docetaxel in NSCLC is underway.

Legal entity responsible for the study: Novocure

Funding: Novocure

Disclosure: M. Giladi, T. Voloshin, O. Talyitzhaki, U. Weinberg, E.D. Kirson: Novocure employee.

1207TiP An open-label, Phase IB study of NEO-PV-01 + Adjuvant with Nivolumab in Patients with Melanoma, Non-Small Cell Lung Carcinoma, or Transitional Cell Carcinoma of the Bladder

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Background: Cancer cells harbor DNA mutations that encode altered amino acid sequences known as neoantigens. Absent from normal tissues and highly specific for tumors, neoantigens bypass central tolerance and have been established as critical targets for tumor directed T cell responses. Tumor mutational burden and neoantigen load have been associated with anti-tumor activity of immune checkpoint inhibitors. Vaccines targeting neoantigens have the potential to induce de novo and expand existing tumor directed T cell responses. NEO-PV-01 is a personalized neoantigen long peptide vaccine designed specifically for the molecular profile of an individual patient's tumor.

Trial design: NT-001 is a single-arm, phase IB study evaluating the safety of administering NEO-PV-01 + adjuvant (Poly-ICLC) with the PD-1 directed antibody, nivolumab, in patients with advanced melanoma, smoking-associated non-small cell lung carcinoma, or transitional cell carcinoma of the bladder who have received no more than one prior systemic treatment. NEO-PV-01 is custom designed and generated for each patient by DNA and RNA sequencing of a recently biopsied tumor, HLA typing, selection of neoantigen epitopes, and synthesis of up to 20 peptides (14-35 amino acids in length). Patients receive treatment with nivolumab at a dose of 240 mg IV q2 weeks while their vaccine is produced. These peptides are formulated into four distinct pools, mixed with Poly-ICLC, and administered subcutaneously into up to 4 non-rotating anatomical sites. Beginning at Week 12, patients receive five priming immunizations over a three-week period followed by booster vaccinations at Weeks 19 and 23 while continuing nivolumab. The primary endpoint is safety. Secondary endpoints are ORR, CBR, PFS, and assessment of response conversion between Week 12 and Week 24. Exploratory endpoints include extensive immune monitoring. The study is open as of October 2016 with estimated enrollment of 90 patients.

Clinical trial identification: NCT02897765

Legal entity responsible for the study: Neon Therapeutics, Inc.

Funding: Neon Therapeutics, Inc.

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1208TiP A phase II exploratory study of durvalumab (MEDI4736) in HIV-1 patients with advanced solid tumors

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Background: Although acquired immunodeficiency syndrome-related mortality is decreasing with the introduction of effective antiretroviral therapy, it has been reported a significant increase in the proportion of non-acquired immunodeficiency syndrome defining malignancies in HIV infected patients, often associated with premature immunosenescence and exhaustion. It has been shown in murine models and humans that programmed cell death ligand 1 (PD-L1) and its receptor, programmed cell death 1 (PD-1) play an active and reversible role mediating T-cell exhaustion both in cancer and in chronic infections. Binding PD-1 to its ligand PD-L1negatively regulates T-cell response, leading to an exhausted phenotype on CD8+ T cells. Therefore, there is a potential of immunotherapeutic intervention targeting PD-1/PD-L1 in order to enhance anti tumoral immune responses as well as to facilitate viral eradication. Durvalumab (MEDI4736) is a human monoclonal antibody (MAb) of the immunoglobulin G1 kappa (IgG1κ) subclass that inhibits binding of programmed cell death ligand 1 (PD-L1) to programmed cell death 1 (PD-1; CD279) and CD80 (B7-1). Durvalumab has demonstrated in cancer patients a favorable safety profile with encouraging antitumor activity, but there are no data about tolerance or anti retroviral activity in HIV patients.

Trial design: This is an ongoing multicenter, open-label, phase 2 study (EUDRACT: 2016-004524-38) whose primary objective is to assess the feasibility of durvalumab at the recommended dose of 1500 mg every 4 weeks in HIV-infected patients with solid tumors for which no additional oncologic standard treatment is available. As secondary objectives the response rate (RECIST 1.1 and irRECIST), duration of response, PFS and OS will be measured. Exploratory objectives include the assessment of antiviral activity by measuring the changes in the HIV viral reservoir, the residual viral replication and the composition and function of circulating T lymphocytes and the study of molecular predictive factors of antitumoral activity on pretreatment tumor samples.

Clinical trial identification: EUDRACT: 2016-004524-38

Legal entity responsible for the study: Spanish Lung Cancer Group

Funding: AZ Spain

Disclosure: All authors have declared no conflicts of interest.

1209TiP A first-in-human, open-label, multicenter phase 1/2a study to evaluate the safety and efficacy of increased repeated doses of the first in class RORγ agonist LYC-55716 in treating locally advanced or metastatic solid tumors

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Background: LYC-55716, a first-in-class oral, small-molecule agonist of nuclear receptor retinoic acid–related orphan receptor γ (RORγ), has been shown in preclinical models to modulate gene expression to reprogram immune cell antitumor effector function and decrease immunosuppressive mechanisms, resulting in immune-mediated tumor growth control and enhanced survival. Data suggest that LYC-55716 acts via well-known antitumor mechanisms by increasing immune cell trafficking and recruitment to tumors, enhancing T cell effector function and memory development, and promoting T cell survival. LYC-55716 may enhance immune-mediated antitumor responses via its effects on T effector/Treg cell ratios, PD-1 expression, and sensitivity to PD-L1 inhibition of T cell proliferation. A first-in-human, single-arm, open-label multicenter Phase 1/2a study is ongoing to evaluate the safety and tolerability of LYC-55716 and determine the maximum tolerated dose and objective response rate. All adult subjects enrolled will have relapsed or refractory metastatic cancer and have failed to responded to standard therapies.

Trial design: The Phase 1 portion of the study will follow a dose-escalation design to evaluate the occurrence of dose-limiting toxicities (DLTs) and determine the maximum tolerated dose and recommended Phase 2 dose of LYC-55716. Following a screening period, adults with locally advanced or metastatic solid tumors will receive 28-day treatment cycles of LYC-55716 BID (n = 4–6/cohort). Dosing escalation considers dose and dosing regimen and is determined by PK profile and safety. Primary endpoints include safety (monitoring of adverse events, physical examination, and lab results) and incidence of DLTs (Grade 3 or 4 toxicities) during the first 28-day treatment cycle. Secondary endpoints include objective tumor response rate as assessed via response evaluation criteria in solid tumors (RECIST) v1.1 assessed at scans performed every 8 weeks, pharmacokinetics, and pharmacodynamics. Results for the first three cohorts of the Phase 1 portion of the study will be available at the time of presentation.

Clinical trial identification: NCT02929862

Legal entity responsible for the study: Lycera Corp.

Funding: Lycera Corp.

Disclosure: H.J. Wilkins: Employee and shareholder of Lycera Corp. All other authors have declared no conflicts of interest.

1210TiP A phase I global trial targeting multiple solid and hematologic malignancies through a NKG2D receptor-based CAR-T immunotherapy

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Background: Because of its increasingly demonstrative successes, CAR-T therapy has been well recognized as one of the most promising therapies for cancer. We have developed a novel autologous CAR-T, NKR-2, incorporating the full-length human natural killer receptor NKG2D fused with the human CD3 zeta signaling domain. When expressed in T-cells, the naturally-expressed DAP10 provides the co-stimulatory signals to NKR-2 to be fully activated. NKR-2 selectively target tumor cells upon recognition of up to eight different NKG2D ligands expressed in many distinct cancer indications. In preclinical studies, NKR-2 demonstrated long-term anti-tumor activity towards multiple solid and hematologic tumors deploying multiple mechanisms of action targeting tumor cells and cells from the neo-vasculature and tumor suppressive immune environment, resulting in an adaptive response. In our recently completed Phase 1 study in hematologic cancers, a single administration of autologous NKR-2 was safe with initial signs of clinical benefit. Likewise, to overcome the operational challenges, our trial design incorporates strategies to harmonize multiple clinical and manufacturing processes while also enhancing patient safety and clinical outcomes.

Trial design: THINK trial (THerapeutic Immunotherapy with NKR-2) is a EU/US open-label Phase I study to assess the safety and clinical activity of NKR-2 therapy administered in three infusions, two weeks apart in five solid tumor indications (CRC, urothelial, TNBC, pancreatic, ovarian) and two hematologic indications (AML/MDS and MM). No lymphodepleting conditioning is required in this study. The study contains two consecutive segments. The dose escalation segment will enroll 18 patients in two separate hematologic and solid malignancy arms, and evaluate 3 dose levels of NKR-2 ($3x10^8$, $1x10^9$ and $3x10^9$ cells per injection) following a 3 + 3 design. The expansion segment will then enroll 96 additional patients in 7 separate cohorts for each indication with 3 steps of statistical analysis (overall futility, futility within each cohort and final evaluation). At time of submission, the trial has completed enrollment in its first cohort among solid indications.

Clinical trial identification: FDA: CYAD-N2T-002

Legal entity responsible for the study: CELYAD

Funding: CELYAD

Disclosure: B. Verma, U. Santanam, C. Lonez, D.E. Gilham, F. Lehmann: Employment with a pharmaceutical company: Employee of Celyad. A. Awada, P. Aftimos, P. Lewalle, N. Meuleman, J-P. Machiels, G. Catala, E. Vandenneste, J. Brayer, D. Sallman, S. Sahebjam, T. Kerre, S. Rottey, K. Odunsi, E.S. Wang: Corporate-sponsored research: Institute has received research finding from Celyad.

1211TiP FAK-PD1: a phase I/IIa trial of FAK (defactinib) & PD-1 (pembrolizumab) inhibition

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Background: Focal Adhesion Kinase (FAK) is a pivotal intracellular mediator of extracellular contact interactions. It is over-expressed in cancer, with a long-established role in migration, invasion & survival, and is associated with poor prognosis. Recently FAK has been found to have a similar activity in recruitment of immunosuppressive cells to the tumour. We have shown that FAK inhibition can re-model the tumour immune microenvironment *in vivo*, shifting the balance from inhibitory Tregs, macrophages, fibroblasts and myeloid progenitors, to one which supports an active CD8+ adaptive immune response, resulting in tumour clearance and lasting immunity. FAK inhibition synergises with Programmed cell death receptor 1 (PD-1) blockade in more resistant models. Defactinib (VS-6063, Verastem) is a small molecule FAK inhibitor in Phase II development with an encouraging safety profile and biological activity. Pembrolizumab (MK-3475, MSD) is a humanized IgG4/kappa monoclonal antibody to PD-1, licensed for the treatment of an increasing number of tumour types. This recently open trial will assess the safety, tolerability and preliminary activity of defactinib plus pembrolizumab in patients with advanced solid malignancies.

Trial design: FAK-PD1 is an open label, phase I/IIa clinical trial, combining 200 mg pembrolizumab as a 3-weekly IV infusion, with defactinib given orally twice daily at either 200 mg or 400 mg, before leading into three tumour-specific expansions (non-small cell lung cancer, mesothelioma and pancreatic cancer) at the selected dose. Up to 60 patients, PS 0-1, with adequate blood parameters, measurable disease, baseline tissue, and without contraindications to either agent, will be treated for up to 2 years until clear clinical progression, unacceptable toxicity, or withdrawal. Primary endpoint is safety (NCI-CTCAE v4.03); secondary endpoints include objective response rate (irRECIST), progression-free survival, FAK Y397 phosphorylation and immune cell infiltrate effects. Exploratory endpoints include comprehensive cellular and molecular characterisation of baseline and on-treatment tumour samples, and serial blood immune cell and cytokine profiling. Positive data will support further development of the combination.

Clinical trial identification: FAK-PD1 EudraCT number: 2015-003928-31

Legal entity responsible for the study: University of Glasgow & NHS Greater Glasgow and Clyde

Funding: Cancer Research UK, Verastem Inc, and Merck Sharp and Dohme Ltd •Verastem Inc (via the Combinations Alliance program) and Cancer Research UK

Disclosure: All authors have declared no conflicts of interest.

1212TiP PIVOT-02: A phase 1/2, open-label, multicenter, dose escalation and dose expansion study of NKTR-214 and nivolumab in patients with select, locally advanced or metastatic solid tumor malignancies

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Background: Abundance and functional quality of tumor infiltrating lymphocytes are positively linked with tumor response and improved survival with checkpoint inhibitors. NKTR-214 is a CD122-biased agonist that targets the IL2 pathway and is designed to provide sustained signaling through the heterodimeric IL2 receptor pathway (IL2Rβɤ) to preferentially activate and expand NK and effector CD8+ T cells over CD4+ T regulatory cells within the tumor microenvironment. NKTR-214 has been administered to 28 patients with advanced cancers. NKTR-214 as a single agent demonstrated a substantial increase in both CD8+ T and NK cells within the tumor microenvironment in patients with prior immune checkpoint therapy (Bernatchez et al 2016). Given the favorable safety profile and strong biomarker data, a trial combining NKTR-214 and nivolumab was initiated.

Trial design: PIVOT-02 is a phase 1/2 open-label trial in patients (pts) with locally advanced or metastatic melanoma (mM), non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), urothelial carcinoma, or triple-negative breast cancer (TNBC). The primary objectives are to evaluate safety and tolerability, determine the recommended phase 2 dose (RP2D), and assess tumor response by RECIST 1.1. In an outpatient setting, NKTR-214 is administered at dose levels of 0.003, 0.006 and 0.009 mg/kg in combination with nivolumab at two flat dose schedules of either 240 mg @ q2w or 360 mg @ q3w. As of May 8, 17 pts (7 mM, 8 RCC, and 2 NSCLC) have been enrolled into 4 cohorts in the dose-escalation phase. In the dose-expansion phase, approximately 250 pts will be enrolled in five tumor types and eight indications; immunotherapy naïve patients and patients who are relapsed/refractory to checkpoint therapy are being studied separately. Extensive blood and tumor tissue samples are being collected to measure immune activation using immunophenotyping including flow cytometry, immunohistochemistry (IHC), T cell clonality and gene expression analyses. Enrollment is ongoing.

Clinical trial identification: NCT02983045

Legal entity responsible for the study: Nektar Therapeutics

Funding: Nektar Therapeutics

Disclosure: A. Diab: Consulting or Advisory Role - Celgene; CureVac; Nektar Research Funding - Celgene (Inst); Idera (Inst); Nektar (Inst); Pfizer (Inst) Travel, Accommodations, Expenses – Nektar. M.E. Hurwitz: Employment - Pfizer Consulting or Advisory Role – Nektar. N. Tannir: Honoraria - Bristol-Myers Squibb; Exelixis; GSK; Nektar; Novartis; Pfizer Advisory Role - Bristol-Myers Squibb; Exelixis; GSK; Nektar; Novartis Research Funding - Bristol-Myers Squibb; Epizyme; Exelixis; Novartis Travel - Bristol-Myers Squibb; Exelixis; GSK; Nektar; Novartis; Pfizer. C. Bernatchez: Employment - Lexicon (I) Stock - Lexicon (I) Advisory Role - Lion Biotechnologies Research Funding - Idera; Nektar Patents - Patent pending on BTLA as a marker for better CD8 T cells for adoptive immunotherapy. C. Haymaker: Cara L. Haymaker Research Funding - Idera; Nektar. B.D. Curti: Honoraria - Prometheus Speakers' Bureau - Prometheus Research Funding - Bristol-Myers Squibb; Galectin Therapeutics; MedImmune; Prometheus; Viralytics Travel, Accommodations, Expenses - Agonox; MedImmune; Nektar; Prometheus. I. Gergel: Employment - Nektar Leadership - Corium International; Nektar Stock and Other Ownership Interests - Corium International; Nektar. M. Tagliaferri: Employment - Nektar Travel, Accommodations, Expenses - Nektar J. Zalevsky: Employment - Nektar. U. Hoch, S. Aung, M. Imperiale: Employment - Nektar Stock and Other Ownership Interests - Nektar D. Cho: Honoraria - Bristol-Myers Squibb; Exelixis; Roche/Genentech Consulting or Advisory Role - Pfizer; Prometheus. S.S. Tykodi: Consulting or Advisory Role - Amgen; Prometheus Research Funding - Argos Therapeutics (Inst); Bristol-Myers Squibb (Inst); Exelixis (Inst); Genentech (Inst); GlaxoSmithKline (Inst); Prometheus (Inst). I. Puzanov: Consulting or Advisory Role - Amgen; Bristol-Myers Squib; Roche/Genentech. H. Kluger: Honoraria - Merck Consulting or Advisory Role - Alexion Pharmaceuticals; Prometheus; Regeneron Research Funding - Merck (Inst) Travel, Accommodations, Expenses - Bristol-Myers Squib P. Hwu: Stock and Other Ownership Interests - immatics; Lion Biotechnologies Consulting or Advisory Role - Lion Biotechnologies Research Funding - Bristol-Myers Squibb (Inst); Genentech (Inst). M. Sznol: Stock -Adaptive Bio; Amphivena; Intensity Thera Advisor - Adaptimmune; Alexion; Amgen; AstraZeneca; Biodesix; Bristol-Myers Squibb; Genentech; Immune Design; Janssen; Kyowa; Lilly; Lion Bios; Lycera; MSD; Merus; Modulate; Nektar; Novartis; Pfizer; Symphogen; Theravance. All other authors have declared no conflicts of interest.

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MELANOMA AND OTHER SKIN TUMOURS

1213O Characterization of complete responses (CRs) in patients with advanced melanoma (MEL) who received the combination of nivolumab (NIVO) and ipilimumab (IPI), NIVO or IPI alone

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Background: In clinical studies, 10-15% of patients (pts) treated with anti-PD-1 monotherapies achieved durable CRs. Combination treatment with NIVO+IPI resulted in higher response rates, longer progression-free survival (PFS), and improved overall survival (OS) vs IPI alone, but with an increased frequency of adverse events (AEs). Here, we characterized CRs among pts who received combination therapy vs NIVO or IPI alone.

Methods: In this post hoc analysis, efficacy and safety data were pooled for NIVO+IPI (N = 409), NIVO (N = 526), and IPI (N = 362) from the phase 2 CheckMate 069, phase 3 CheckMate 066, and phase 3 CheckMate 067 studies in pts with MEL. Across studies, the minimum duration of follow-up was 24 months (median ~31 months).

Results: In the pooled analysis, the CR rate was 18% for NIVO+IPI, 16% for NIVO, and 4% for IPI, with partial responses (PRs) in 41%, 28%, and 14% of pts, respectively (Table). Among the 75 CR pts in the NIVO+IPI cohort, the majority (77%) are off treatment and 8% received a subsequent systemic therapy; 15% had elevated LDH levels and 32% had M1c disease. Median duration of CR has not been reached, with 63/75 pts (84%) remaining in response. After an additional follow-up of 12 months (from the 1-year initial follow-up), 24/166 pts (14%) with a PR converted to a CR. For the 75 CR pts in the NIVO+IPI cohort, 2-year PFS and OS rates were 86% and 92%, respectively. Treatment-related AEs of grade 3-4 occurred in 60% of NIVO+IPI-treated pts with a CR, 65% with a PR, and in 60% with stable disease; 31%, 36%, and 35%, respectively, led to discontinuation. There were no treatment-related deaths.

Table: 1213O

	NIVO+IPI (N = 409)	NIVO (N = 526)	IPI (N = 362)
Objective response rate (%)	58.9	43.9	18.0
CR, n (%)	75 (18)	83 (16)	14 (4)
PR, n (%)	166 (41)	148 (28)	51 (14)
Pts remaining in response (CR)	63/75 (84%)	75/83 (90%)	11/14 (79%)
CR pts continuing on treatment	17/75 (23%)	41/83 (49%)	4/14 (29%)
CR pts not continuing on treatment	58/75 (77%)	42/83 (51%)	10/14 (71%)

Conclusions: MEL pts treated with NIVO+IPI had a high rate of durable CRs, with the majority remaining in response and often not requiring additional treatment at a median follow-up of ~31 months. Some pts with a PR convert to a CR over time. Updated analyses based on 3-year data will be presented.

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Legal entity responsible for the study: Bristol-Myers Squibb

Funding: Bristol-Myers Squibb

Disclosure: C. Robert: Served as a consultant for Amgen, Bristol-Myers Squibb, Merck, and Roche; paid honoraria from Amgen, Bristol-Myers Squibb, GSK, Merck, Novartis, and Roche. J. Larkin: Received research funding from Bristol-Myers Squibb, MSD, Novartis, and Pfizer; travel funding from Bristol-Myers Squibb, GSK, MSD, Esai, Pfizer, and Roche. P.A. Ascierto: Served as a consultant for Amgen, Array, Bristol-Myers Squibb, Merck-Serono, MSD, Novartis, Pierre-Fabre, and Roche-Genentech; institution received research funding from Array, Bristol-Myers Squibb, and Roche-Genentech. G.V. Long: Served as a consultant for Amgen, Bristol-Myers Squibb, Merck, MSD, Novartis, Pierre-Fabre, and Roche; paid honoraria from Bristol-Myers Squibb, Merck, MSD, and Roche. J.C. Hassel: Funding for trial procedures according to study protocol from Bristol-Myers Squibb; honoraria from Amgen, Bristol-Myers Squibb, GSK, MSD, Novartis, and Roche; research grant/funding from Bristol-Myers Squibb; travel funding from Amgen, Bristol-Myers Squibb, GSK, MSD, Novartis, and Roche. D. Schadendorf: Served as a consultant or advisor for Roche/Genentech, Novartis, Bristol-Myers Squibb, Merck Sharp & Dohme, Merck Serono, Sysmex, Amgen, Grunenthal Group, Immunocore; participated on a speakers' bureau for Roche, Bristol-Myers Squibb, Merck Sharp & Dohme, Novartis, Amgen, Incyte, Pierre Fabre; travel funding from Roche/Genentech, Bristol-Myers Squibb, Amgen, Merck, Merck Serono, Novartis; paid honoraria from Roche/Genentech, Novartis, Amgen, Bristol-Myers Squibb, Merck Sharp & Dohme, Sysmex, Immunocore, Grunenthal Group, Merck Serono, Agenus, Array BioPharma, LEO Pharma, Incyte, Pfizer, Pierre Fabre, Philogen, Regeneron; received institutional research funding from Bristol-Myers Squibb and Novartis. F.S. Hodi: Consultant: Amgen, EMD Serono, MSD, Novartis, Roche-GNE; travel funding: Bristol-Myers Squibb and Novartis; patent pending royalties per institutional policy; other: B Bristol-Myers Squibb MS; institutional research funding: Bristol-Myers Squibb, MSD, Novartis, Roche-GNE. C. Lebbé: Served on an advisory board for Bristol-Myers Squibb, GSK, MSD, Novartis, and Roche. J-J. Grob: Served as a consultant to Amgen, Bristol-Myers Squibb, GSK, Merck, Novartis, and Roche; participated on speakers' bureau for Bristol-Myers Squibb, GSK, and Roche; travel funding from Roche; recipient of research funding from Bristol-Myers Squibb and Roche. J. Wagstaff: Honoraria from Astellas, Bristol-Myers Squibb, Merck, Novartis, Pfizer, and Roche; consultant to Astellas, Bristol-Myers Squibb, Merck, Novartis, Pfizer, and Roche; served on speakers' bureaus for Astellas, Bristol-Myers Squibb, and Novartis; travel funding from Astellas, Bristol-Myers Squibb, and Novartis. J. Chesney: Served as a consultant to Bristol-Myers Squibb; received research funding from Bristol-Myers Squibb. D. Hogg: Served as a consultant to Bristol-Myers Squibb, GSK, Novartis, and Roche. O. Bechter: Served as a consultant or advisor to Bristol-Myers Squibb; and received travel funding from Roche. I. Márquez-Rodas: Honoraria from Bristol-Myers Squibb, MSD, Novartis, and Roche; served as a consultant to Amgen, Bioncotech, Bristol-Myers Squibb, MSD, Novartis, and Roche; travel funding from Amgen, Bristol-Myers Squibb, and MSD. D. Walker: Employee of Bristol-Myers Squibb; immediate family member has stock or other ownership in Antares Pharma. R. Bhore: Employee of and owns stock in Bristol-Myers Squibb. M.A. Postow: Served on an advisory board for Bristol-Myers Squibb; recipient of research grant support from Bristol-Myers Squib. J.D. Wolchok: Consultant: Bristol-Myers Squibb, GSK, Jounce, MedImmune, Merck, Polaris, Polynoma, and Ziopharm; research funding: Bristol-Myers Squibb, GSK, MedImmune, and Merck; patent issued for DNA vaccine of cancer in companion animals (co-investor). All other authors have declared no conflicts of interest.

1214O Epacadostat plus pembrolizumab in patients with advanced melanoma: Phase 1 and 2 efficacy and safety results from ECHO-202/KEYNOTE-037

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Background: Tumors can evade immunosurveillance through upregulation of indoleamine 2,3-dioxygenase 1 (IDO1). Epacadostat (E) is a potent, selective inhibitor of the IDO1 enzyme. The combination of E + the PD-1 inhibitor pembrolizumab (P) is being evaluated in an open-label, phase 1/2 study in multiple tumor types (ECHO-202/KEYNOTE-037). We report phase 1 and 2 efficacy and safety data for patients (pts) with advanced melanoma (27Feb2017 data cutoff).

Methods: Pts previously treated with checkpoint inhibitors were excluded. Pts received E (25, 50, 100, or 300 mg PO BID) + P (2 mg/kg or 200 mg IV Q3W) during phase 1.

MTD was not exceeded. E (100 mg BID) + P (200 mg Q3W) was selected for phase 2. Responses were assessed in RECIST 1.1 evaluable pts.

Results: 64 pts enrolled (phase 1, n = 22; phase 2, n = 42). Median age, 65; male, 70%; BRAF+, 30%; M1c disease, 52%. Median duration of follow-up was 253+ days (range, 5 to 904+ days). Among 54 efficacy evaluable pts, ORR was 56% (30/54; 8 CR, 22 PR) and DCR (CR+PR+SD) was 78% (42/54). In treatment-naïve pts (n = 45), ORR was 56% (25/45; 6 CR, 19 PR) and DCR was 78% (35/45). Among treatment-naïve pts receiving E 100 mg BID (n = 30), ORR was 60% (18/30; 2 CR, 16 PR). Responses were observed regardless of PD-L1 and BRAF mutation status. At data cutoff, 28/30 responses in the melanoma cohort were ongoing (median duration of response = 287.5+ days, range 1+ to 763+ days). Median PFS was 12.4 mo; PFS rates at 6, 12, and 18 mo were 70%, 54%, and 50%, respectively. In treatment-naïve pts, median PFS has not been reached; PFS rates at 6, 12, and 18 mo were 68%, 52%, and 52%. The most common (>15%) all-grade treatment-related AEs (TRAEs) were fatigue (39.1%), rash (32.8%), pruritus (26.6%), and arthralgia (15.6%). Grade ≥3 TRAEs were observed in 17.2% of pts (most common: lipase increased, n = 4; rash, n = 3; and amylase increased, n = 2). 3 pts discontinued for TRAEs (lipase increased, n = 1; arthralgia, n = 2). No treatment-related deaths occurred. Biomarker evaluation is ongoing.

Conclusions: Consistent with the phase 1 results, E + P continues to be well tolerated and showed promising clinical activity. A phase 3 study in pts who are treatment-naive for advanced melanoma is ongoing (NCT02752074).

Clinical trial identification: NCT02178722

Legal entity responsible for the study: Incyte Corporation, Wilmington, DE

Funding: Incyte Corporation, Wilmington, DE; Merck & Co., Inc., Kenilworth, NJ

Disclosure: O. Hamid: Advisory Board - Merck & Co., Inc, Amgen, Novartis, Roche, Bristol-Myers Squibb; Corporate-sponsored Research - Incyte Corporation (Institution), Merck & Co., Inc. (Institution); Speaker's Bureau – Bristol-Myers Squibb, Genetech, Novartis, Amgen; Honoraria – Genetech, Bristol-Myers Squibb, Novartis. T.F. Gajewski: Advisory Board - Merck & Co., Inc; Corporate-sponsored Research - Incyte Corporation (Institution), Merck & Co., Inc. (Institution). T.M. Bauer: Corporate-sponsored Research - Incyte Corporation (Institution), Merck & Co., Inc. (Institution) A.J. Olszanski: Advisory Board - Merck & Co., Inc, Bristol-Myers Squib; Corporate-sponsored Research - Incyte Corporation (Institution), Merck & Co., Inc. (Institution), Bristol-Myers Squibb, Novartis, Teva, Takeda, Pfizer; Other Substantive Relationships - Data Safety Monitoring Board: Takeda. J.J. Luke: Consult: Amgen, Array, AstraZeneca, BeneVir, Bristol-Myers Squibb, Castle, CheckMate, EMD Serono, Gilead, Novartis, Merck; Inst res supp: AbbVie, BostonBiomedical, Bristol-Myers Squibb, Celldex, Corvus, Delcath, 5Prime, Genentech, Immunocore, Incyte, Intensity, MedImmune, Macrogenics, Novartis, Pharmacyclics, Merck, Tesaro. A.S. Balmanoukian: Corporate-sponsored Research – MedImmune/AstraZeneca, Merck Serono, Genentech, Incyte Corporation (Institution), Merck & Co., Inc. (Institution); Other Substantive Relationships - Speaker's Bureau at Bristol-Myers Squibb, Merck, Genentech, AstraZeneca. E.V. Schmidt: Employment and stock ownership at Merck & Co., Inc. B. Sharkey, J. Maleski, M.J. Jones: Employment and stock ownership at Incyte Corporation T.C. Gangadhar: Corporate-sponsored Research - Incyte Corporation (Institution), Merck & Co., Inc. (Institution), Bristol-Myers Squibb, Roche, Cerulean; Honoraria - Merck & Co., Inc., Novartis; Advisory Role - Bristol-Myers Squibb All other authors have declared no conflicts of interest.

1215O Results of COLUMBUS Part 2: A phase 3 trial of encorafenib (ENCO) plus binimetinib (BINI) versus ENCO in BRAF-mutant melanoma

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Background: The addition of a MEK inhibitor (MEKi) to a BRAF inhibitor (BRAFi) in *BRAF* V600-mutant metastatic melanoma improves efficacy, including progression-free survival (PFS) and objective response rate (ORR), and attenuates some BRAFi–associated toxicities. Part 1 of the COLUMBUS study met its primary endpoint. The BRAFi ENCO 450 mg once daily (QD) + the MEKi BINI 45 mg twice daily (BID; COMBO450) improved PFS vs vemurafenib (VEM) alone and ENCO 300 mg QD (ENCO300) alone in patients (pts) with advanced *BRAF* V600-mutant melanoma. The tolerability of COMBO450 was favorable compared with VEM or ENCO300. In Part 2, the contribution of BINI to the combination was further evaluated by maintaining the same dose of ENCO in the combination (ENCO 300 mg QD + BINI 45 mg BID; COMBO300) and comparator arms (ENCO300 alone; ClinicalTrials.gov, NCT01909453; EudraCT, 2013-001176-38).

Methods: Pts were randomized 3:1 to COMBO300 or ENCO300. Data from ENCO300 arms in Parts 1 + 2 were combined for the primary efficacy comparison of PFS by independent blinded central review (BCR). Other analyses included PFS for COMBO300 vs ENCO300 (Part 2 only), ORR, complete response (CR) and partial response (PR) by BCR and local review, and safety.

Results: Pt characteristics are presented in the Table. Median PFS (95% CI) for COMBO300 was 12.9 mo (10.1–14.0) vs 9.2 mo (7.4–11.0) for ENCO300 (Parts 1 + 2) and 7.4 mo (5.6–9.2) for ENCO300 (Part 2). The hazard ratio (HR) for COMBO300 was 0.77 (0.61–0.97; P = 0.029, 2-sided) vs ENCO300 (Parts 1 + 2) and 0.57 (0.41–0.78; $P<0.001$, 2-sided) vs ENCO300 (Part 2). ORR, CR, and PR by BCR/local review (%) were 66/72, 8/11, and 58/62 for COMBO300, 50/56, 5/8, and 45/49 for ENCO300 (Parts 1 + 2), and 50/53, 3/3, and 47/50 for ENCO300 (Part 2). Safety profiles were consistent with Part 1 (Table).

Table: 1215O COLUMBUS Part 2: Baseline Characteristics, Duration of Exposure, and Safety

	COMBO300	ENCO300 (Parts 1 + 2)	ENCO300 (Part 2 only)
	n = 258	n = 280	n = 86
Patient characteristics			
Baseline ECOG PS1, %	26	28	28
Baseline LDH high, %	31	28	37
Stage M1c disease at study entry, %	67	64	67
Tolerability			
Median duration of exposure, wk	52	32	32
AEs leading to discontinuation, %	12	13	10
AEs requiring dose modification, %	45	69	63
AEs requiring additional therapy, %	82	94	92
AEs (all-grade; ≥20% in any group), %			
Diarrhea	28	12	7
Nausea	27	36	29
Arthralgia	22	43	42
Fatigue	22	26	30
Increased creatine phosphokinase	20	1	0
Vomiting	15	25	19
Myalgia	14	27	23
Alopecia	13	49	33
Headache	12	26	23
Pain in extremity	11	20	14
Grade 3/4 AEs (≥5% in any group), %			
Increased alanine aminotransferase	5	<1	0
Increased creatine phosphokinase	5	0	0
Increased gamma-glutamyltransferase	5	4	2
Palmar-plantar erythrodysesthesia syndrome	<1	11	5
Arthralgia	1	8	5
Myalgia	<1	8	5

Conclusions: COMBO300 meaningfully improved PFS, ORR, and tolerability vs ENCO300, confirming the contribution of BINI to both efficacy and safety.

Clinical trial identification: Trial protocol number, CMEK162B2301 (release date, July 13, 2015)

Legal entity responsible for the study: Array BioPharma Inc

Funding: Array BioPharma Inc and Novartis Pharmaceuticals Corporation

Disclosure: R. Dummer: Honoraria from and consulting/advisory role for Roche, Bristol-Myers Squibb, GSK, MSD, Novartis, and Amgen; research funding from Roche, Bristol-Myers Squibb, GSK, MSD, and Novartis. P.A. Ascierto: Consulting fees from Bristol-Myers Squibb, Roche/Genentech, MSD, Ventana, Novartis, Amgen, and Array BioPharma; research funding from Bristol-Myers Squib, Roche/Genentech, Ventana, and Array BioPharma H. Gogas: Consultant for Roche, Bristol-Myers Squibb, MSD, Novartis, and Amgen. A. Arance: Honoraria from and consulting/advisory role and speakers bureau for Novartis, Roche, MSD, and Bristol-Myers Squibb; travel expenses from Roche and Bristol-Myers Squibb. M. Mandala: Honoraria from Novartis, GSK, Bristol-Myers Squibb, MSD, and Roche; speakers bureau for Novartis, GSK, Roche, and Bristol-Myers Squibb; advisory board member for Novartis, Amgen, MSD, and Bristol-Myers Squibb; research funding from Roche. C. Garbe: Honoraria and travel expenses from and served in a consulting/advisory role and speakers bureau member for Amgen, Bristol-Myers Squibb, MSD, Novartis, Roche, and Philogen; research funding for University Hospital Tübingen from Bristol-Myers Squibb, Novartis, and Roche. D. Schadendorf: Honoraria and travel expenses from and consulting/advisory role and speakers bureau for Amgen, Bristol-Myers Squibb, Novartis, Roche, and MSD; research funding for University Hospital Essen from Amgen, Bristol-Myers Squibb, Novartis, Roche, and MSD. I. Krajsová: Advisory board member for Bristol-Myers Squibb, Novartis, Roche, MSD; travel expenses from Bristol-Myers Squibb and MSD. R. Gutzmer: Consulting fees and/or honoraria from Roche, Bristol-Myers Squibb, MSD, GSK, Novartis, Almirall, LEO, Amgen, Pfizer, Merck Serono, Boehringer Ingelheim; research funding from Roche, Novartis, Pfizer, Pierre Fabre, Johnson & Johnson; travel expenses from Bristol-Myers Squibb, Roche. V. Chiarion Sileni: Honoraria received from Novartis, GSK, Bristol-Myers Squib, MSD, and Roche; speakers bureau for Novartis, GSK, Roche, and Bristol-Myers Squibb; advisory board member for Novartis, Amgen, MSD, Bristol-Myers Squibb, and Roche. J.W.B. de Groot: Consulting/advisory role for Amgen, Bayer, Celgene, Roche, Bristol-Myers Squibb, GSK, MSD, and Merck Serono. N. Yamazaki: Advisory role for Chugai Pharma, Bristol-Myers Squibb Japan, and Ono Pharmaceutical; honoraria from Chugai Pharma, Bristol-Myers Squibb Japan, Ono Pharmaceutical, GlaxoSmithKline, Takeda, AstraZeneca Japan, Boehringer Ingelheim, and Maruho. C. Loquai: Advisory board member for Roche, Novartis, Bristol-Myers Squibb, MSD, BioNTech, Pierre Fabre, and Amgen; speakers fees from Roche, Novartis, B Bristol-Myers Squibb MS, and MSD; travel expenses from Roche, Novartis, Bristol-Myers Squibb, MSD, and Amgen. L.A. de Parseval: Employee of Novartis Pharma AG; may own stock or stock options. M. Pickard: Employee of Array BioPharma; may own stock or stock options. V. Sandor: Employee/leadership role at Array BioPharma; stock or other ownership of Array BioPharma and Incyte Corp. C. Robert: Consultant for Roche, Novartis, Bristol-Myers Squibb, MSD, and Amgen. K.T. Flaherty: Honoraria from and consulting/advisory role for Novartis and Array BioPharma; research funding from Novartis. All other authors have declared no conflicts of interest.

1216O KEYNOTE-022 update: phase 1 study of first-line pembrolizumab (pembro) plus dabrafenib (D) and trametinib (T) for BRAF-mutant advanced melanoma

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Background: Combination of anti–PD-1 agents with BRAF/MEK inhibitors (i) may provide synergistic antitumor effects in *BRAF*-mutant melanoma. The ph 1/2 KEYNOTE-022 study (NCT02130466) is assessing safety and antitumor activity of recommended doses of pembro + BRAFi D + MEKi T; updated and additional ph 1 results are reported.

Methods: Treatment-naive pts with $BRAF^{V600E/K}$-mutant stage III/IV melanoma received pembro 2 mg/kg Q3W + D 150 mg BID + T 2 mg QD. Primary end point was safety; AEs were graded per CTCAE v4.0. Efficacy end points were ORR, PFS, and OS. Data cutoff: Mar 1, 2017.

Results: Of the 15 pts enrolled, 10 (66.7%) had PD-L1+ tumors (≥1% staining), 13 (86.7%)/2 (13.3%) had ECOG PS 0/1, and 1 (6.7%) had stable brain metastases. Median follow-up was 19.7 mo (range, 15.9-31.1). 3/15 (20.0%) pts had DLTs (pt 1 had gr 4 neutropenia; pt 2 had gr 4 ALT increase; and pt 3 had gr 4 ALT, gr 3 AST, and gr 3 GGT increase); all resolved. Thus, this dose was the MTD and recommended ph 2 regimen. 11 (73%) pts had gr 3-4 TRAEs; ALT increase, AST increase, and pyrexia occurred in ≥ 20% of pts. 7 (46.7%) pts had immune-mediated AEs, most commonly hyperthyroidism in 3 pts (2 gr 1 and 1 gr 2) and hypothyroidism in 4 pts (all gr 1). Treatment was discontinued (d/c) for 2 events (1 gr 2 pneumonitis and 1 gr 3 autoimmune hepatitis) and was interrupted for 3 events (1 gr 1 hyperthyroidism, 1 gr 2 anterior uveitis, and 1 gr 3 erythematous rash); all resolved. ORR (RECIST v.1.1, investigator; confirmed + unconfirmed) was 67%; 1 pt had CR, 9 had PR; an additional 2 pts had SD and 3 had PD. ORR (RECIST v.1.1, investigator; confirmed only) was 53%; 8 pts had PR; an additional 3 pts had SD and 4 had PD. Median time to response was 2.8 mo (range, 2.2-3.0); median DOR was not reached (range, 2.8-26.5 mo). Among the 8 pts with confirmed ORR, 6 had ongoing responses and 2 had progression at data cutoff. 2 pts remained on triplet therapy, 2 d/c D + T, and 4 d/c pembro + D + T as of last follow-up.

Conclusions: Updated results show that approved doses of pembro + D + T continue to demonstrate promising antitumor activity for *BRAF*-mutant melanoma. A randomized ph 2 study is currently evaluating this triplet regimen as first-line therapy for *BRAF*-mutant melanoma.

Clinical trial identification: NCT02130466, May 1, 2014

Legal entity responsible for the study: Merck & Co., Inc., Kenilworth, NJ, USA

Funding: Merck & Co., Inc., Kenilworth, NJ, USA

Disclosure: A. Ribas: Stock ownership with Kite Pharma; honoraria with Amgen, Pfizer, Roche, and Merck F.S. Hodi: Advisory board member with Merck, Genentech, Novartis, EMD Serono, and Amgen; research funding from Bristol-Myers Squibb. V. Atkinson: Advisory board member with MSD, Novartis, and Pierre Fabre; speakers' bureau involvement with MSD, Bristol-Myers Squibb, and Novartis; honoraria with MSD, Bristol-Myers Squibb, and Novartis; travel expenses from MSD, Bristol-Myers Squibb, and Novartis. M.S. Carlino: Advisory board member with Bristol-Myers Squibb, Merck, Amgen, and Novartis; honoraria from Merck and Bristol-Myers Squibb. G.V. Long: Advisory board member with Amgen, Bristol-Myers Squibb, Array, Merck MSD, Novartis, Pierre-Fabre, and Roche; honoraria from Bristol-Myers Squibb, Roche, and Merck MSD. W.H. Miller: Consultant fees from Bristol-Myers Squibb, Roche, Novartis, Merck, GSK, and Amgen. Y. Huang: Employment with Novartis. B. Homet Moreno: Employment with Merck; stock ownership with Merck. N. Ibrahim: Employment with Merck; stock ownership with Merck and GSK. O. Hamid: Advisory board member Amgen, Novartis, Roche, Bristol-Myers Squib, Merck; speakers' bureau Bristol-Myers Squibb, Genentech, Novartis, Amgen; research funding AstraZeneca, Bristol-Myers Squibb, Celldex, Genentech, Immunocore, Incyte, Merck, Merck Serono, MedImmune, Novartis, Pfizer, Rinat, Roche. All other authors have declared no conflicts of interest.

1217PD Comprehensive genomic profiling (CGP) and tumor mutational burden (TMB) assessment in subtypes of metastatic melanoma

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Background: Metastatic melanoma (MM) is widely treated with both kinase inhibitors and immunotherapies, providing meaningful survival benefit. Contrasting CGP and TMB results across MM subtypes provides a blueprint for rational decision making in light of increasing effective therapeutic options.

Methods: CGP for 2,225 MM evaluated up to 315 genes plus introns of 28 genes commonly rearranged in cancer using hybrid-capture, adaptor ligation-based libraries (mean coverage >620X). TMB was calculated from ~1.1 Mb of sequenced DNA. Base substitutions, insertions and deletions (short variants; SV); rearrangements; and copy number changes were assessed.

Results: We evaluated 9 MM subtypes: routine cutaneous (CT), desmoplastic (DM), acral lentiginous (AL), Spitzoid (SP), gynecologic mucosal (GMC), head and neck mucosal (HN), anorectal (ARM) and ocular (OC). Each group harbored characteristic genomic alterations (GA) (Table). *BRAF* was mutated in 38% of CT (92% SV; 8% amplifications, fusions or cases with >1 *BRAF* GA). Patients with TMB ≥20 mut/Mb were common in CT and DM, but 5% or less in all other subtypes. The frequency of *BRAF* GA was lower in AL, GMC, HN, ARM and OC. SP commonly harbored fusions in *BRAF* (60%) and other kinases. *KIT* GA were prominent in GMC and AL. Key findings include novel drivers of BRAF inhibitor resistance including *BRAF* rearrangements, kinase duplications and MEK GA.

Conclusions: In the largest cohort of MM with CGP to date, genomic profiles and TMB differ across MM subtypes. Highly prevalent BRAF GA in CT and high TMB in CT and DM permit effective use of targeted and immunotherapies, although novel BRAF inhibitor resistance mechanisms were observed. In addition, a variety of non-BRAF kinase targets are apparent in some MM subtypes.

Table: 1217PD

	CT	DM	AL	SP	GMC	HN	ARM	OC
Samples	1991	12	22	22	44	22	7	105
BRAF GA	38%	0%	18%	60% (Fusion)	15%	13%	0%	2%
Other driver GA	*NF1* (21%) *PTEN* (12%) *KIT* (5%)	*TP53 (75%) NF1 (50%)*	*NF1* (18%) *PTEN* (18%) *KIT* (18%)	Fusions in: *ROS1* (3%) *RET* (3%) *NTRK1* (1%) *ALK* (1%)	*NF1* (32%) *KIT* (25%) *PTEN* (13%)	*NF1* (18%) *PTEN* (9%) *EGFR* (5%) *NTRK1* (5%)	*NF1* (43%) *NTRK1* (14%) *BRCA2* (14%)	*NF1* (2%) (*BAP1*, *GNAQ*, *GNA11* or *MYC* found in 100%)
TMB ≥10 mut/Mb	61%	92%	NA	NA	3%	5%	14%	3%
TMB ≥20 mut/Mb	42%	83%	NA	NA	0	5%	0%	1%

Legal entity responsible for the study: Jeffrey S Ross

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Disclosure: J.S. Ross: Employee, leader and owns stock in Foundation Medicine J.A. Elvin: Employee and owns stock in Foundation Medicine J-A. Vergilio, J. Suh, S. Ramkissoon, E. Severson, S. Daniel, S.M. Ali, A.B. Schrock, D. Fabrizio, G.M. Frampton, L.M. Gay: Employee and owns stock in Foundation medicine V.A. Miller, P.J. Stephens: Employee, leader and owns stock in Foundation medicine All other authors have declared no conflicts of interest.

1218PD Precision medicine for the treatment of metastatic uveal melanoma: A pilot study

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Background: There is no standard active treatment for metastatic uveal melanoma. Precision medicine with high-throughput genomics could improve the outcome of patients suffering of "hard-to-treat" cancer.

Methods: Metastatic uveal melanoma included in the prospective TREAT20Plus study had fresh tumor biopsies that were subjected to a complete genomic analysis program (WGS, whole exome seq, RNAseq, Methylome, Proteome and cell culture). Integrative data analysis was performed and generated a comprehensive molecular tumor analysis (CMTA). An interdisciplinary molecular tumour board interpreted the data and provided treatment recommendations.

Results: Thirteen patients (6 F, 7 M) were biopsied. Age: 68 (33-81). Site of biopsy: soft tissue: 5, liver: 4, lung: 2, pleura: 1, lymph node: 1. Pre-treatment number: 2 (0-4) and type: iv chemotherapy: 10, checkpoint Inh:6, intra-hepatic: 8. Genomic results were available in the first 10 patients within 34 days (31-40). The number of mutations was low: median 25 (16-44.). Mutations were found in *GNAQ*: 11, *GNA11*: 6, *BAP1*; 3, *SF3B1*: 4. We detected one gene-fusion: *ZNF704-PKIA*. The most frequent gene overexpression affected the following genes: *MYC*: 7, *MET*: 5, *BCL2*: 4, *CCND2*: 1, *ERBB3*: 1. There was a loss of expression of: *CDKN2A*: 2, *PTEN*: 1, *EFS*: 1. A slightly up-regulated expression of *ALK* was detected in one patient and confirmed as an oncogenic ALK^{ATI} isoform that originates from an alternative internal transcription start site in intron 19. At time of recurrence a second biopsy showed a complete loss of *CDKN2A* expression through a bi-allelic loss of chromosome 9. Treatment recommendations were the following: inhibitor of MEK: 10, of MET: 5, of CDK4/6: 3, of ALK: 1, of PI3K: 1. Treatment was initiated in 7 patients: 5 received Trametinib, one patient each received Palbociclib, Crizotinib or Cabozantinib, respectively. Among the 6 currently evaluable patients one showed minor response (15%), one a stable disease, one progressive disease, and 3 patients cannot yet be evaluated.

Conclusions: Genomic integrative analysis showed a net advantage over exome-only or panel sequencing. This strategy is clinically feasible and led to individualized treatment recommendations. Treatment outcome will be presented for the whole cohort.

Legal entity responsible for the study: Charité Comprehensive Cancer Center

Funding: German Federal Ministry of Research and Education (BMBF) grant Nr. 031A512 Max Planck Society

Disclosure: M. Schuette, C. Wierling, B. Lange: Employees of Alacris Theranostics. T. Kessler: Employee of Alacris Theranostics GmbH. F. Kiecker: Advisory Boards: Novartis, Bristol-Myers Squibb, MSD, Roche, Amegen, Merck Serono. H. Lehrach: Board of direction of Alacris Theranostics. U. Keilholz: Speaker honoraria and advisory board roles are with AstraZeneca, Bristol-Myers Squibb, Merck, MSD, Pfizer, Novartis, Innate Corporate-sponsored research is with AstraZeneca and Merck. All other authors have declared no conflicts of interest.

1219PD Combined radiofrequency ablation and ipilimumab in uveal melanoma: Results from the SECIRA-UM trial

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Background: After enucleation or radiotherapy of the primary lesion, 50% of uveal melanoma (UM) patients develop distant metastases. In contrast to cutaneous melanoma, targeted therapies and checkpoint inhibitors failed to improve overall survival (OS) in UM. Chemoembolization or intrahepatic artery perfusion improved local control, but failed to show OS benefit. The anti-CTLA-4 antibody ipilimumab (IPI), showed limited clinical activity in UM, thus combination therapies may be required. Preclinical experiments in a murine melanoma model indicated that additional radiofrequency ablation(RFA) enhanced antigen presentation and induced durable responses.

Methods: We therefore have set-up a phase 1b/2 study to assess safety and efficacy of the combination of RFA and IPI in UM patients with at least 2 unresectable liver lesions. In the phase 1b part patients underwent RFA of one liver lesion and received 4 courses IPI 0,3mg/kg, 3mg/kg or 10mg/kg q3wk in a 3 + 3 design. Primary endpoint of the phase 1b part was safety in terms of dose limiting toxicities per cohort to define the recommended phase 2 dose(RP2D). Primary endpoints of the phase 2 part were confirmed objective response rate (ORR) and disease control rate (DCR) according to RECIST 1.1 (only non-RFA lesions), secondary endpoints were progression free survival (PFS) and OS.

Results: IPI 10mg/kg + RFA was defined as the RP2D. After 19 patients had been treated, the study was amended to adjust the RP2D to IPI 3mg/kg + RFA, because 9 patients (47%) had developed grade 3 colitis. In the 3mg/kg IPI + RFA cohort also 19 patients have been treated, and baseline characteristics were balanced between the cohorts. Treatment related grade ≥3 AEs were seen in 53% of patients in the 10mg/kg cohort versus 32% in the 3mg/kg cohort. No confirmed objective responses were observed; the confirmed DCR was 21% in the 10mg/kg cohort and 11% in the 3mg/kg cohort. Median PFS was 2.8 months and was comparable for both groups, median OS was 13.6 months for the 10mg/kg cohort versus 9.5 months for the 3mg/kg cohort ($p = 0.23$).

Conclusions: The combination of IPI 3mg/kg +RFA was safe but showed limited clinical activity in UM. However, overall survival seems to be longer compared to other study cohorts of UM patients, especially in the IPI 10mg/kg cohort.

Clinical trial identification: EudraCT Number: 2011-004200-38

Legal entity responsible for the study: NKI-AVL

Funding: Bristol-Myers Squibb

Disclosure: J.V. Thienen: Advisory board: MSD, Bristol-Myers Squibb. J.B. Haanen: Advisory role: Bristol-Myers Squibb. MSD, Pfizer, Roche, Novartis, Neon Therapeutics Research grants: Bristol-Myers Squibb, MSD, GSK. C.U. Blank: Advisory board: Bristol-Myers Squibb, MSD, Novartis, GSK, Pfizer, Lilly, Roche Research grant: Bristol-Myers Squibb, Novartis. All other authors have declared no conflicts of interest.

1220PD Phase 2 study of neoadjuvant dabrafenib + trametinib (D+T) for resectable stage IIIB/C BRAF V600 mutant melanoma

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Background: Combination D+T improves the overall survival (OS) of patients (pts) with BRAF V600 mutant advanced melanoma, and an adjuvant trial is in progress (NCT01682083). We sought to explore neoadjuvant D+T for pts with bulky but resectable stage III melanoma.

Methods: In this phase 2 study, 35 pts received standard dose D+T for 12 wks prior to complete resection of the pre-therapy tumour bed (RES), then 40 wks of further D+T. Eligible pts had ECOG PS ≤ 1 with histologically confirmed resectable bulky AJCC v7 stage IIIB/C BRAF V600 mutant melanoma. CT and PET scans were performed at baseline and 12 wks just prior to RES for RECIST and metabolic complete response (rCR and mCR respectively). CT monitoring was continued 12 wkly thereafter to 2 yrs then 6 monthly to 3 yrs. Biopsies were taken at baseline and wk 1. The primary endpoints were the complete pathological response (pCR) and RECIST response rate (rRR) at wk 12. Secondary endpoints were surgical morbidity, mCR, relapse free survival (RFS), OS, toxicity and translational endpoints.

Results: At data cut 18th April 2017, 35 had commenced D+T. 33 had reached RES (27 stage IIIC [8 in-transit only], 6 IIIB; 32 V600E, 1 V600K; 12 LDH >ULN). At RES, 17/33 (52%) had pCR, 16 (48%) had rCR (rRR 88%), and 16 (48%) had mCR. The pathologic response was discordant with RECIST response in 7 (21%) pts and metabolic response in 9 (27%) pts; only 11 (65%) pts with pCR had rCR and mCR. No pt discontinued D+T and no pt progressed during the neoadjuvant period, D+T did not make surgery more difficult in any pt, and in 16 (48%) surgery was deemed easier. Median F/U post RES was 12.1 mo (95% CI 8.8-14.8). 12 (36%) pts had recurred (median 12.9 mo), 4 while on D+T, 6 with prior pCR, 8 at distant sites, and 1 pt had died. 26 (79%) pts developed drug fever. 18 (55%) had ≥ 1 surgical complication post RES; 11 had a wound infection requiring antibiotics, 5 had a seroma, 2 bled. Updated data will be presented including tumour biopsy and and ctDNA biomarker data.

Conclusions: Neoadjuvant D+T has a high response rate and high pCR rate in resectable stage III melanoma. Surgical complication rates were consistent with historic controls and stage of disease.

Clinical trial identification: NCT01972347

Legal entity responsible for the study: Melanoma Institute Australia

Funding: Novartis

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1221PD (Neo-)adjuvant ipilimumab + nivolumab (IPI+NIVO) in palpable stage 3 melanoma – updated relapse free survival (RFS) data from the OpACIN trial and first biomarker analyses

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Background: The combination of IPI+NIVO induces high response rates and improved overall survival in late stage melanoma. T cell checkpoint inhibition is of greatest value at the moment of TCR triggering and therefore dependent on the amount of antigen present, indicating that adjuvant immunotherapy will work most efficiently, when initiated prior to surgery.

Methods: Two-arm Phase 1b feasibility trial consisting of 20 high risk AJCC stage 3B/C melanoma patients with palpable nodal disease receiving the combination of IPI 3mg/kg and NIVO 1mg/kg, either adjuvant four courses after surgery, or split neo-adjuvant and adjuvant.

Results: In this update 20 patients are evaluable. Neo-adjuvant application of IPI+NIVO was feasible and no surgery-associated adverse events were attributed to (neo-) adjuvant therapy. 18/20 patients had to stop earlier due to grade 3/4 toxicities. Neo-adjuvant IPI+NIVO reduced tumor load in 8/10 patients (3 pCR, 4 near pCRs [minimal remaining micro metastases], 1 pPR [<50% vital tumor cells], 1 pSD and 1 pPD). So far, none of the responders in the neo-adjuvant arm has relapsed. Relapse was observed for the 2 non-responders within the neo-adjuvant arm and for 3 patients within the adjuvant arm. We will present at ESMO 2017 the 18 months RFS update and in detail the biomarker analyses. Latter comprises RNA sequencing and Nanostring™ microscope spatial profiling to identify biomarkers for response, and TCR sequencing, with the aim to distinguish T cell responses between both, the two treatment arms and between patients relapsing or remaining free of disease.

Conclusions: The combination of IPI+NIVO in the (neo-)adjuvant treatment setting for high risk stage 3 melanoma patients is promising and currently tested in an international phase 2 randomized trial comparing different combination schemes (OpACIN-neo trial, NCT02977052) with the aim of preserving efficacy, but reducing toxicity. Biomarkers identifying patients responding upon neo-adjuvant IPI+NIVO and remaining relapse-free for a long time, will help to select the patients that need to be exposed to IPI+NIVO associated toxicity.

Clinical trial identification: NCT02437279

Legal entity responsible for the study: NKI-AVL

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Disclosure: P. Kvistborg: Advisory board: Neon therapeutics, Merck, Personalis. J.V. Thienen: Advisory board: MSD, Bristol-Myers Squibb. B. Stegenga, B. Lamon: Employee of Bristol-Myers Squibb. J.B. Haanen: Advisory role: Bristol-Myers Squibb, MSD, Pfizer, Roche, Novartis, Neon Therapeutics Research grants: Bristol-Myers Squibb, MSD, GSK. C.U. Blank: Advisory role: Bristol-Myers Squibb, MSD, GSK, Roche, Novartis, Lilly, Pfizer Research grants: Bristol-Myers Squibb, Novartis. All other authors have declared no conflicts of interest.

1222PD Regional differences in overall survival (OS) in patients with advanced melanoma (MEL) who received nivolumab (NIVO) combined with ipilimumab (IPI) or NIVO alone in a phase 3 trial (CheckMate 067)

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Background: NIVO+IPI and NIVO significantly improved PFS and OS vs. IPI alone in the CheckMate 067 study. Descriptively, NIVO+IPI showed longer OS than NIVO (hazard ratio: 0.88), with 2-year OS rates of 64% and 59%, respectively. Post-hoc analyses by region were performed to evaluate potential differences between patients (pts) treated in the EU and those treated in the USA.

Methods: Baseline patient characteristics, safety and efficacy were evaluated in the two highest enrolling regions (EU, 55% and USA, 22%) using data from the CheckMate 067 study. Minimum follow-up of the pts was 28 months.

Results: EU pts were more likely to have M1c disease than USA pts (60% vs 53%), and more likely to have *BRAF* wild-type (WT) tumors (69% vs 59%). In a multivariate analysis, which adjusted for baseline factors, the only significant interaction between NIVO+IPI and NIVO was by region. Adjusted hazard ratios (HRs) for OS in the NIVO+IPI vs NIVO groups were 0.90 (0.66–1.23) for the EU and 0.53 (0.29–0.98) for the USA. Across all arms, 2-year OS rates were lower in the EU vs USA pts, particularly for pts with *BRAF* WT tumors (Table). In pts with *BRAF* mutant tumors, similar OS outcomes were observed between regions. Treatment exposure, safety, management of adverse events, and use of subsequent therapies did not differ substantially between the two regions. Objective response rates and progression-free survival were also similar between the two regions.

Conclusions: Differences in OS between the EU and the USA appear to be largely due to poorer survival outcomes in EU pts with BRAF WT tumors, which likely impacted OS differences between NIVO+IPI and NIVO in the overall population. Additional analyses by region, the first report of 3-year OS, as well as analyses by tumor mutational burden will be presented. Acknowledgement: J. Larkin and J.D. Wolchok contributed equally to this study.

Clinical trial identification: NCT01844505

Table: 1222PD

2-yr OS rates	ITT Population		EU						USA					
			Overall		*BRAF* WT		*BRAF* Mutant		Overall		*BRAF* WT		*BRAF* Mutant	
	N	Rate	N	Rate	N	Rate	N	Rate	N	Rate	N	Rate	N	Rate
NIVO+IPI	314	64%	177	60%	122	55%	55	73%	64	78%	40	77%	24	79%
NIVO	316	59%	170	56%	107	52%	63	63%	68	64%	52	63%	16	67%
IPI	315	45%	170	40%	114	38%	56	45%	75	52%	50	53%	25	50%
HR	0.88		0.90		1.03		0.69		0.53		0.61		0.65	
(95% CI)*	(0.69–1.12)		(0.66–1.23)		(0.72–1.48)		(0.37–1.30)		(0.29–0.98)		(0.30–1.23)		(0.20–2.13)	

*NIVO+IPI vs NIVO.

Legal entity responsible for the study: Bristol-Myers Squibb

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1223PD Quality-adjusted survival of combined nivolumab plus ipilimumab (NIVO+IPI) or NIVO alone vs IPI among treatment-naïve patients (pts) with advanced melanoma (MEL): a quality-adjusted time without symptoms or toxicity (Q-TWiST) analysis

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Background: We compared quality-adjusted survival (OS) of combined NIVO+IPI or NIVO alone vs IPI among treatment-naïve pts with advanced MEL enrolled in the CheckMate 067 trial.

Methods: The Q-TWiST approach was used to partition OS into 3 health states: time without disease progression or symptoms of toxicity (TWiST), time with grade ≥3 treatment-related AE toxicity after randomization but before progression (TOX), and time after progression (REL). Q-TWiST was calculated by multiplying mean time spent in each state at 36 months (mos) by their utility (TWiST=1.0, TOX=0.5, and REL=0.5). Q-TWiST differences were assessed at various times ranging from 3 to 36 mos. A ≥ 15% relative Q-TWiST gain (vs mean IPI OS) was considered clearly clinically important.

Results: Compared with IPI, NIVO+IPI pts had longer (difference in mean mos, 95% CI) TWiST (9.6, 7.4 to 11.7) and TOX (0.3, 0.1 to 0.4) but shorter REL time (-5.2, -7.1 to -3.2). Compared with IPI, NIVO pts had a longer TWiST (7.3, 5.0 to 9.6), shorter REL time (-3.4, -5.5 to -1.3), and shorter TOX (-0.1, -0.2 to 0.1). Q-TWiST was highest for NIVO+IPI, followed by NIVO, and IPI (Table). Relative Q-TWiST gains were also favorable for NIVO+IPI (+34.0% v IPI) and NIVO (+26.4% v IPI) and increased as follow-up increased from 3 to 36 months for all comparisons.

Conclusions: At 36 months, NIVO and NIVO+IPI pts had a clinically important improvement in Q-TWiST vs IPI. As these benefits continue to accrue over time, future analyses with longer follow-up are planned.

Table: 1223PD

Mean (95% CI) time, mos

	NIVO+IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
TOX	0.6 (0.4 to 0.7)	0.2 (0.1 to 0.3)	0.3 (0.2 to 0.4)
TWiST	19.1 (17.4 to 20.8)	16.8 (15.1 to 18.5)	9.5 (8.1, 10.9)
REL	6.1 (4.7 to 7.6)	7.9 (6.5 to 9.3)	11.3 (9.8 to 12.8)
Q-TWiST	22.4 (21.0 to 23.9)	20.9 (19.4 to 22.3)	15.3 (14.1 to 16.5)

Clinical trial identification: QoL study based on the 067 trial NCT01844505 protocol number is CA209-067 (CheckMate 067)

Legal entity responsible for the study: Bristol-Myers Squibb

Funding: Bristol-Myers Squibb

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1224PD Analysis of response and survival in patients (pts) with ipilimumab (ipi)-refractory melanoma treated with pembrolizumab (pembro) in KEYNOTE-002

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Background: Treatment with checkpoint inhibitors can result in durable responses and deepening of responses over time with conversion of SD to PR or CR, and PR to CR. In the randomized KEYNOTE-002 study (NCT01704287), pembro 2 mg/kg or 10 mg/kg improved PFS (HR 0.57 and 0.50; $P<0.0001$ for both) vs chemo in pts with ipi-refractory melanoma. In this post hoc analysis, we assessed evolution of response and survival for 361 pembro-treated pts.

Methods: Pts were treated until disease progression (PD), unacceptable toxicity or investigator/pt decision. Response (RECIST v1.1; investigator review) was assessed at wk 12, every 6 wk until wk 48, then every 12 wk, and confirmed by subsequent scan. Survival was assessed every 12 wk during follow-up. Pembro arms were combined given no difference in efficacy of doses.

Results: As of 3 Feb 2017, median follow-up duration was 42.7 mo. In pembro-treated pts, median PFS was 4.2 mo (95% CI 3.3-5.6), and 36-mo PFS rate was 16%. Median OS was 14.0 mo (11.8-16.2), and 36-mo OS rate was 30%. 99 of 361 pts had CR (n = 29) or PR (n = 70) for ORR of 27.4% (95% CI 22.9-32.3); 88 pts had SD. Median time to response was 2.9 mo. Of 29 pts with CR, 5 converted from SD, 21 from PR. Of 70 pts with PR, 28 converted from SD. Median time from SD to PR was 2.7 mo (range 0.9-25.2), from SD to CR was 6.9 mo (3.9-21.9), and from PR to CR was 8.0 mo (1.4-25.2). Median DOR was not reached in pts with CR or PR (Table). Median duration of SD was 6.9 mo (range 0.8+ to 38.8+). 9 (31%) pts with CR, 28 (40%) with PR and 63 (72%) with SD had subsequent PD; in these pts, median duration of CR was 17.1 mo (5.5-36.1), PR 7.7 mo (2.0-31.8), and SD 5.8 mo (2.7-25.3). Median PFS and OS were longer in pts with CR or PR (Table).

Conclusions: Responses to pembro are durable and associated with prolonged OS in ipi-refractory melanoma. Even in these heavily pretreated pts best response can evolve over time, with late conversions from SD to PR/CR and PR to CR observed.

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Legal entity responsible for the study: Merck & Co., Inc.

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1225PD Prognostic impact of early complete metabolic response on FDG-PET, in BRAF V600 mutant metastatic melanoma patients treated with combination vemurafenib & cobimetinib

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Background: Imaging with FDG-PET allows early recognition of metabolic response to targeted agents. We evaluated the timing of complete metabolic response (CMR) on PET as a predictor of clinical outcome in BRAF V600 mutant melanoma patients treated with vemurafenib and cobimetinb, as part of the BRIM-7 trial.

Methods: BRAF inhibitor naïve patients from BRIM-7 were included if they had evaluable PET scans at baseline, in cycle 1 (C1) (D10-15) and in C2 (D35-49). Metabolic response was evaluated by percentage injected dose (%ID). 52 of 63 BRAF-naïve patients were eligible for analysis (3 excluded - no C1 scan; 6 no C2 scan; 2 unevaluable scans due to excessive physiological muscle uptake). The primary aim was to evaluate the prognostic significance of an early CMR to combination vemurafenib and cobimetinib therapy. We divided patients into 3 groups, based on timing of CMR attainment.

Results: 13 patients achieved CMR in cycle 1 (CMR1), 15 patients achieved CMR in cycle 2 (CMR2) and 24 patients did not achieve CMR within the first 2 cycles of treatment (noCMR). The median, 2 year and 3 year progression free survival (PFS) and overall survival (OS) of the 3 above groups are summarized in Table.

Table: 1224PD

Outcomes	CR (n = 29)	PR (n = 70)	SD (n = 88)	All-treated (N = 361)
Median time to response*, mo (range)	2.9 (2.4-24.9)	2.9 (1.9-27.9)	–	2.9 (1.9-27.9)
Median DOR, mo (range)	NR (5.5-41.6+)	NR (1.9+ to 43.5+)	6.9 (0.8+ to 38.8+)†	NR (1.9+ to 43.5+)
Median PFS, mo (95% CI)	41.0 (38.9-NR)	35.8 (27.9-NR)	7.0 (5.8-9.7)	4.2 (3.3-5.6)
12/24/36-mo PFS rate‡	97%/75%/72%	76%/66%/49%	24%/6%/1%	29%/21%/16%
Median OS, mo (95% CI)	NR (NR-NR)	NR (NR-NR)	16.5 (13.8-20.5)	14.0 (11.8-16.2)
12/24/36-mo OS rate‡	100%/93%/89%	96%/86%/71%	71%/31%/24%	55%/37%/30%

*Best overall response with confirmation;
†Duration of SD;
‡Kaplan-Meier method for censored data; CI, confidence interval; NR, not reached

Table: 1225PD

	CMR1	CMR2	No CMR
Median PFS (yrs)	Not reached	1.1	1.0
2 yr PFS (%, 95% CI)	83.9 (65.7-100)	13.3 (3.7-48.4)	37.5 (22.4-62.9)
3 yr PFS (%, 95% CI)	71.9 (48.8-100)	13.3 (3.7-48.4)	18.8 (7.9-44.5)
Median OS (yrs)	Not reached	2.4	2.5
2 yr OS (%, 95% CI)	84.6 (67.1-100)	63.0 (41.5-95.8)	58.3 (41.6-81.8)
3 yr OS (%, 95% CI)	74.0 (52.2-100)	21.0 (6.3-70.2)	30.9 (16.5-57.9)

Patients achieving CMR1 had significantly better outcome than patients achieving CMR2 in terms of PFS (HR 0.18, 95% CI 0.05-0.62) and OS (HR 0.23, 95% CI 0.06-0.85). Similar results were observed comparing CMR1 over no CMR in PFS (HR 0.19, 95% CI 0.06-0.64) and in OS (HR 0.25, 95% CI 0.07-0.87). There was no difference between the CMR2 and noCMR groups in terms of PFS or OS.

Conclusions: Attainment of CMR on an early D10-14 PET was highly predictive of long-term survival with BRAF and MEK inhibition. However, attainment of CMR at a later time point at D35-49 did not appear predictive of a survival benefit. In fact, no difference in PFS or OS could be observed in patients who achieved CMR at D35-49, compared to those patients who did not attain CMR. Correlative science analysis to investigate the mechanism of these observations are underway.

Clinical trial identification: number: NCT01271803

Legal entity responsible for the study: Genentech Roche

Funding: Genentech Roche

Disclosure: J. Frederickson: Employer of Genentech and has Roche stocks D. Colburn, N. Choong, M. Wongchenko: Employee of Roche-Genentech. All other authors have declared no conflicts of interest.

1226PD Five-year efficacy and safety update from METRIC: Trametinib vs chemotherapy in patients with BRAF V600E/K–mutant advanced or metastatic melanoma

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Background: BRAF mutations are found in 50% of patients (pts) with advanced melanoma. Previously, the METRIC trial (NCT01245062) demonstrated that the MEK inhibitor trametinib (T) increased PFS in this population of patients with a clinical benefit that could last ≥ 2 yrs in some pts. We report findings from the 5-year follow-up analysis

Methods: METRIC is an open-label, randomized Ph3 study of pts who received ≤ 1 prior regimen of chemotherapy (C) for histologically confirmed unresectable stage IIIC or IV cutaneous BRAF V600E/K–mutant metastatic melanoma (MM). Pts were randomized (2:1) to T (2 mg/day) or intravenous C (dacarbazine [1000 mg/m^2] or paclitaxel [175 mg/m^2] every 3 wks). Pts were stratified according to baseline lactate dehydrogenase level and previous C for advanced disease. Pts who progressed on C were allowed to crossover and receive T. The primary endpoint was progression-free survival (PFS); secondary endpoints included overall survival (OS), duration of response and safety.

Results: 322 pts (V600E: 281, 600K: 40, V600E/K mutation: 1) were enrolled (T: 214; C: 108). At data cutoff (Dec 16, 2016), median follow-up was 12.3 months (mo). The median OS for the T arm was 15.6 mo vs 11.3 mo for the C arm (HR = 0.84 [95% CI, 0.63–1.11], P = 0.19). Landmark OS for the T arm vs the C arm at 1, 2, 3, and 5 yrs were 60.9% vs 49.6%; 32.0% vs 29.4%; 20.6% vs 22.6%; and 13.3% vs 17.0%, respectively. Most pts (n = 70, 65%) in the C arm crossed over and received T. Median time to crossover was 3.1 (1–20) mo; median duration of follow-up after crossover was 8.8 (0–67) mo. Among pts who received post-tx anti-cancer therapy (n = 208), most received targeted therapy (n = 118), immunotherapy (n = 90), or C (n = 84). No new safety signals were observed.

Conclusions: This is the longest reported follow up for T monotherapy in pts with BRAF V600E/K–mutant MM and demonstrates that some of these pts experience long-term benefit with targeted therapy. Pts with extended follow-up after initiation of T, contributed to long-term survival for those randomized to the C arm.

Clinical trial identification: NCT01245062

Legal entity responsible for the study: Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA

Funding: Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA

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1227P Avelumab treatment in chemotherapy-naïve patients with distant metastatic Merkel cell carcinoma (mMCC)

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Background: MCC is a rare, aggressive skin cancer. In a phase 2 study of patients with mMCC progressed on or after chemotherapy (JAVELIN Merkel 200; NCT02155647), avelumab (a human anti–PD-L1 antibody) showed durable responses and a manageable safety profile, including an objective response rate (ORR) of 33.0%, proportion of responses with ≥1-year duration of 74% (Kaplan-Meier estimate), and estimated 1-year overall survival (OS) rate of 52%. Based on these results, avelumab was approved by the US FDA in March 2017 and is the only approved treatment for patients with mMCC. Here, we report early interim results from patients with mMCC receiving first-line avelumab.

Methods: Eligible patients with mMCC and no prior systemic treatment for metastatic disease received avelumab 10 mg/kg Q2W. Tumors were assessed every 6 weeks (RECIST v1.1) by independent review committee (IRC). Adverse events (AEs) were assessed by NCI CTCAE v4.0.

Results: At data cutoff on Dec 30, 2016, 29 of 112 planned patients had been enrolled. Median follow-up was 3.1 months (range 0.3–8.5) and median duration of treatment was 8.1 weeks (range 2.0–37.9). Of 16 patients with ≥13 weeks of follow-up, confirmed ORR by IRC was 62.5% (95% CI 35.4–84.8) with response ongoing in all 10 patients, including in all 5 patients with ≥6 months of follow-up. Of 25 patients with ≥6 weeks

of follow-up, unconfirmed ORR by IRC was 68.0% (95% CI 46.5–85.1); responses were ongoing at last follow-up in 16 of 17 responders (94.1%; 1 censored due to other therapy). 23 of 29 patients (79.3%) had a treatment-related AE (TRAE), including 5 (17.2%) with a grade 3 or 4 TRAE. There was 1 immune-mediated TRAE (grade 1 rash). 5 patients (17.2%) discontinued avelumab due to a TRAE. There were no treatment-related deaths. Updated analyses of 39 patients will be presented (n = 29 and n = 14 with ≥13 weeks and ≥6 months of follow-up, respectively; data cutoff Mar 24, 2017), including PFS and OS analyses.

Conclusions: First-line avelumab treatment resulted in early responses and a high ORR in distant mMCC, substantiating prior findings with second-line or later avelumab treatment. Most responses were ongoing, including all responders with ≥6 months of follow-up. Enrollment is ongoing.

Clinical trial identification: NCT02155647 EMR100070-003

Legal entity responsible for the study: Merck KGaA, Darmstadt, Germany; Pfizer Inc, New York, NY, USA.

Funding: Merck KGaA, Darmstadt, Germany; Pfizer Inc, New York, NY, USA.

Disclosure: S.P. D'Angelo: Provided a consultant/independent contractor role for EMD Serono, Pfizer and Nektar. J. Russell: Provided consulting/independent contractor role to EMD Serono. J. Hassel: Received research funding from Bristol-Myers Squib, provided an advisory role to Amgen and MSD, and received honoraria from Bristol-Myers Squibb, MSD, Roche and Novartis. C. Lebbé: Advisory/consulting role for Roche, Bristol-Myers Squib, Novartis, Amgen, MSD, GSK. Research funding from Roche and Bristol-Myers Squibb. Speaker's Bureau's for Bristol-Myers Squib, Amgen, Roche, Novartis. Honoraria from Roche, Bristol-Myers Squibb, Novartis, Amgen. Travel accommodation from Roche. Bristol-Myers Squibb, Novartis. B. Chmielowski: Provided an advisory role for EMD Serono, Merck, Bristol-Myers Squibb, Genentech, Immunocore and Eisai. Also served as a consultant/independent contractor for Amgen and has participated in speaker's bureau's for Janssen and Genentech. G. Rabinowits: Institution has received research funding from EMD Serono, Exelixis and Millennium. GR has provided a consulting/advisory role and has received honoraria from EMD Serono. P. Terheyden: Provided an advisory role for Bristol-Myers Squibb, Merck, Novartis and Roche. Has also received honoraria from Bristol-Myers Squibb, Novartis and Roche. I. Zwiener: Employee of Merck KGaA, Darmstadt, Germany. M. Bajars: Employee of Merck Serono SIA. M. Hennessy: Employee of EMD Serono Inc, Billerica MA, USA. H.L. Kaufman: Consultancy for and honoraria from Amgen, Celldex, Compass Therapeutics, EMD Serono, Turnstone Biologics, Prometheus, Sanofi, Merck KGaA,. Research funding from Amgen, EMD Serono, Viralytics, Prometheus, Merck KGaA. Speakers bureau for Merck KGaA. All other authors have declared no conflicts of interest.

1228P Long-term effects of sonidegib on tumor burden: 30-month results from the phase 2 randomized bolt trial

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Background: Sonidegib, a hedgehog pathway inhibitor (HPI), is approved in the United States and European Union for locally advanced basal cell carcinoma (laBCC) based on primary results from the BOLT trial (Migden, *Lancet*, 2015). Updated data from 30-months analysis demonstrated continued efficacy and manageable safety (Dummer ASCO 2016). Here we present 30-month tumor burden results, which have not previously been presented or published.

Methods: Eligible HPI-treatment-naïve patients with laBCC not amenable to curative surgery/radiotherapy or patients with metastatic BCC (mBCC) were randomized 1:2 to receive sonedegib 200 or 800 mg QD. For all patients, tumor burden was assessed as decrease of best percentage change from baseline by central review. For patients with laBCC, tumor lesions were assessed by photography and modified RECIST criteria; for patients with mBCC, photography or MRI/computed tomography (CT) and RECIST 1.1 were used.

Results: Evaluable patients at 30 months were from the primary efficacy analysis set (pEAS) for laBCC patients (200 mg, n = 32; 800 mg, n = 74) and mBCC patients (200 mg, n = 12; 800 mg, n = 19). Consistent with the primary, 12- and 18-month analyses, 96.9% (n = 31) and 94.6% (n = 70) of patients with laBCC experienced a substantial reduction in tumor size with sonidegib 200 and 800 mg, respectively. Reduction in target lesions for patients with mBCC receiving 200 mg was 91.7% (n = 11) across all time points; for the 800 mg group, 84.2% (n = 16) of patients experienced reduction in tumor lesions in the primary, 12-, 18-month analyses and 89.5% (n = 17) at 30 months. Sonidegib 200 mg had a more favorable safety profile compared to 800 mg, with lower rates of grade 3/4 adverse events (AEs; 43.0% vs 64.0%) and AESs events leading to discontinuation (30.4% vs 40.0%).

Conclusions: Sonedegib 200 and 800 mg in patients with laBCC and mBCC demonstrated substantial target tumor lesion reduction across 30 months. Safety/tolerability was manageable and similar across 30 months with no new side effects emerging following the primary analysis.

Clinical trial identification: NCT01327053

Legal entity responsible for the study: Novartis Pharmaceuticals

Funding: Sun Pharmaceutical Industries Ltd.

Disclosure: R. Dummer: Received research funding from Novartis, Merck, Bristol-Myers Squibb, Roche, and GlaxoSmithKline and has served as a consultant/advisory board for Novartis, Merck, Bristol-Myers Squibb, Roche, GlaxoSmithKline, Amgen, and Takeda. M. Migden: Participated on advisory boards and received honoraria from Genentech, Inc.; Novartis Pharmaceuticals Corporation; Eli Lilly and Company; and Sun Pharmaceuticals

1230P Modulation of Risk and Prognosis of Cutaneous Melanoma Patients by Genetic Polymorphisms on PDCD1 Gene

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Background: This study aimed to evaluate whether PD1.1 (c.-606G>A), PD1 (c.627 + 252C>T), PD1.5 (c.804C>T) and PD1.9 (c.644C>T) single nucleotide polymorphisms (SNPs) on *PDCD1* gene influence risk, clinicopathological aspects and survival of patients with cutaneous melanoma (CM).

Methods: We evaluated 250 CM patients diagnosed at the University of Campinas and 250 blood donors (controls). DNA was analyzed by real-time polymerase chain reaction (PCR) for genotyping. *PDCD1* gene expression and PD1 protein expression were assessed by quantitative PCR and flow cytometry, respectively. The statistical significance of differences between groups was calculated using the Fisher's exact or chi-square test. Bonferroni method was used in multiple comparisons. *PDCD1* expression and PD1 expression on T lymphocytes were calculated, using Kruskal-Wallis and Mann-Whitney test, respectively. The prognostic impact of SNPs on recurrence-free survival (RFS) and overall survival (OS) of CM patients were examined using the Kaplan Meier and Cox analyses.

Results: Individuals with PD1 CC genotype isolated and associated with PD1.5 CC genotype were under 2.20 (95% CI: 1.00-4.82, $P = 0.04$) and 2.51 (95% CI: 1.04-6.03, $P = 0.03$) times greater risks of developing CM, respectively. Individuals with phototype I or II and PD1 CC genotype or PD1 CC plus PD1.5 CC genotype had 5.89 and 6.71 more chances of presenting CM than others, respectively. PD1.5 TT genotype was associated with increased expression of *PDCD1* gene when compared with CT or CC genotype ($P = 0.03$). PD1.5 CT or TT genotypes and T allele increased expression of PD1 protein in $CD4^+$ lymphocytes ($P = 0.01$, $P = 0.006$; respectively). At 60 months of follow-up, shorter RFS was observed in patients with PD1.1 AA genotype (33.3% *vs* 72.5%, $P = 0.02$). Patients with PD1.1 AA genotype had 4.39 more chances of presenting tumor progression or relapse in univariate Cox analysis ($P = 0.04$) and patients with PD1.5 CC genotype had 2.38-fold increased risk of evolving to death in multivariate Cox analysis ($P = 0.02$).

Conclusions: The data suggest, for the first time, preliminary evidence that inherited abnormalities in regulation of T lymphocyte activities, related to PD1.1, PD1 and PD1.5 SNPs, alter CM risk and prognosis.

Legal entity responsible for the study: Faculty of Medical Sciences, University of Campinas

Funding: São Paulo Research Foundation (FAPESP)

Disclosure: All authors have declared no conflicts of interest.

1231P Role of an intronic polymorphism in the CREB1 gene, involved in melanogenesis, with the risk and the aggressiveness of cutaneous melanoma

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Background: Recently, we observed 12,882 new single nucleotide polymorphisms (SNPs) associated with cutaneous melanoma (CM) risk in 103 patients and 103 controls, using large-scale genotyping with microarrays. CREB1 c.303 + 373G>A, involved in melanogenesis and located in regulatory sequence of mRNA processing (splicing), was selected for further analyses. An in silico analysis showed that referred SNP may alters the binding sites of splicing regulatory proteins, such as SF1 and hnRNP A1. However, the role of this SNP in the risk, aggressiveness and prognosis of CM is unknown. Verify whether the distinct genotypes of CREB1 c.303 + 373G>A influence the CM risk and prognosis, clinicopathological aspects, and CREB1, SF1 and HNRNPA1 mRNA levels.

Methods: Genomic DNA of 262 patients and 280 controls was analyzed by RT-PCR. Patients were treated with conventional procedures. Gene expressions were determined

by qPCR using total RNA of 56 controls. Chi-square, logistic regression model, Mann-Whitney and Student's t tests analyzed the differences between groups. Progression-free survival (PFS) and overall survival (OS) times were calculated using Kaplan-Meier and Cox regression analyses.

Results: CREB1 GA or AA genotypes were more frequent in CM patients than in controls (72.0% vs. 61.1%, P = 0.02). Carriers of the genotypes were under 1.61-fold increased risk of CM (95% CI: 1.07-2.41) than others. An excess of CREB1 AA variant genotype was seen in patients with Breslow's thickness higher than 1.5mm (28.2% vs. 18.5%, P = 0.04) and high Clark's level (26.2% vs. 13.3%, P = 0.02). The median of follow-up of CM patients was 76 months; no association of referred SNP and patients' PFS and OS was observed in this study. Individuals with CREB1 GA or AA genotypes presented higher mRNA expression of CREB1 (0.94 vs. 0.60 arbitrary units (UAs), P = 0.007), SF1 (1.33 vs. 1.05 UAs, P = 0.03) and HNRNPA1 (0.77 vs. 0.57 UAs, P = 0.02) than those with GG wild-type genotype.

Conclusions: Our data suggest, for the first time, that CREB1 c.303 + 373G>A SNP is an important hereditary factor for the risk and aggressiveness of CM, possibly due to variation of the splicing factors.

Legal entity responsible for the study: University of Campinas

Funding: Foundation for protection of research in the state of São Paulo (FAPESP)

Disclosure: All authors have declared no conflicts of interest.

1232P Investigation of AMBRA1 as a melanoma susceptibility gene

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Background: Melanoma is the most lethal form of skin cancer, which shows a rapid increase in incidence in many countries including Sweden. To date, the annual increase is over 5% and there is an urgent need to improve possibilities for prevention and early diagnoses when the prognosis is far favorable compared to disseminated disease. Melanoma is caused by an interplay of environmental and genetic factors and is one of the cancer forms showing highest heritability. Still a substantial extent of the genes underlying melanoma susceptibility is unknown.

Methods: We have executed whole-exome sequencing of melanoma-prone families to identify novel melanoma predisposing genes. Further genetic and functional studies of strong candidate genes using patient samples and melanoma cell lines has been performed. Various in vitro assays have been used to determine the role of these genes in for example autophagy and cell proliferation.

Results: One gene discovered was the autophagy/beclin-1 regulator 1 (AMBRA1), where a putative splice variant was co-segregating with the melanoma phenotype in a 4-case family. This mutation was not found among over 6000 Swedish population-based controls nor in any additional melanoma patients. AMBRA1 is essential in the regulation of autophagy and apoptosis and has been suggested to function as a tumor suppressor. By gene expression analysis we identified several transcripts of AMBRA1, with differential expression in melanoma tumors and in various melanoma cell lines. In tumor material from the splice variant carrier AMBRA1 showed low levels of expression. In melanoma cell lines, AMBRA1 was up-regulated when adding an autophagy activating reagent while down-regulated when treating the cells with Chloroquine, a drug inhibiting autophagy. AMBRA1 was also significantly up regulated when treating the cells with Crizotinib, a drug that targets the tyrosine kinase receptor c-MET and may induce autophagy, whereas no effect was seen when using the BRAF-inhibitor Vemurafenib. Thus, AMBRA1 may be involved in the Crizotinib-induced autophagy pathway.

Conclusions: Preliminary data suggest AMBRA1 as a candidate melanoma susceptibility gene with a role during autophagy in melanoma cells. Further studies are needed to elucidate the specific role of this gene in melanoma development.

Legal entity responsible for the study: Karolinska Institutet

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Disclosure: All authors have declared no conflicts of interest.

1233P Influence of an intronic polymorphism in the MITF gene, of melanogenic pathway, in the risk and the prognosis of cutaneous melanoma

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Background: We identified more than 12,000 new single nucleotide polymorphisms (SNPs) associated with cutaneous melanoma (CM) risk in 103 patients and 103 controls, using large-scale genotyping with DNA microarrays. A bioinformatics analysis showed that MITF c.938-325G>A SNP, involved in melanogenesis and located in regulatory sequence of mRNA processing (splicing), may alter the binding sites of splicing proteins, such as SF1 and hnRNP A1. However, the role of this SNP in the risk and prognosis of CM patients is still unknown. We aim to evaluate the influence of this SNP on the risk and prognosis of CM, clinical and tumor characteristics, and MITF, SF1 and HNRNPA1 levels.

Methods: MITF genotypes of 262 CM patients and 280 controls were identified in DNA by RT-PCR. Patients were treated with conventional protocols. Gene expressions were evaluated by qPCR using RNA of 73 controls. The differences between groups were assessed by chi-square, logistic regression, t test and ANOVA. Progression-free (PFS) and overall survival (OS) times were estimated by Kaplan-Meier and Cox methods.

Results: The frequency of the AA variant genotype was higher in patients than in controls (26.8% vs. 21.1%, P = 0.03). Individuals with referred genotype were under 1.60-fold increased risk of CM (95% CI: 1.02-2.52) than others. The frequency of GA or AA genotypes was more common in patients with lower phototype (I-III) (90.8% vs. 80.9%, P = 0.04) and with vertical tumors (83.7% vs. 67.5%, P = 0.04). The median of follow-up was 76 months. At 60 months, PFS (53.4% vs. 71.6%, P = 0.005, Cox: HR: 1.84, P = 0.006) and OS (76.2% vs. 82.4%, P = 0.02, Cox: HR: 1.79, P = 0.03) were shorter in patients with AA genotype than others. We observed similar frequencies of MITF (1.2 vs. 1.1 vs. 1.0 arbitrary units (AUs), P = 0.30), SF1 (1.1 vs. 1.2 vs. 1.0 AUs, P = 0.94) and HNRNPA1 (1.1 vs. 1.3 vs. 1.3 AUs, P = 0.61) mRNA levels in individuals with distinct genotypes.

Conclusions: Our results suggest, for the first time, that MITF c.938-325G> SNP is an important inherited factor for the risk and prognosis of CM. Our findings, once validated in additional studies, will contribute to personalize the therapy of CM patients.

Legal entity responsible for the study: University of Campinas (UNICAMP)

Funding: São Paulo Research Foundation (FAPESP)

Disclosure: All authors have declared no conflicts of interest.

1234P Hybrid-capture based genomic profiling identifies BRAF V600 and non-V600 alterations in melanoma samples negative by prior testing

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Background: BRAF and MEK inhibitors are approved for V600-mutated melanoma, and response rates of up to 70% are seen for patients with V600 mutations. Responses to targeted therapies have also been observed for a variety of non-V600 BRAF alterations. Thus, sensitive, accurate, and broad detection of BRAF alterations is critical to match patients with available targeted therapies.

Methods: Pathology reports were reviewed for 385 consecutive melanoma cases (Mar 2016 - Mar 2017) with BRAF mutations or rearrangements identified using a hybrid-capture based next generation sequencing (NGS) assay during the course of clinical care.

Results: Records of prior BRAF molecular testing were available for 79 (21%) cases, utilizing PCR (n = 30), Sanger sequencing (n = 13), IHC (n = 10), non-hybrid capture based NGS (n = 9), or other or unspecified methodology (n = 17). Of cases with BRAF V600 mutations 11/57 (19%) with available data were negative by prior BRAF testing, including 2/11 (18%) with confirmation that the same biopsy was tested. In cases with BRAF V600 mutations, there was no significant difference in mutant allele frequencies (median 35% vs. 40%, p = 0.25) or percentage of tumor nuclei (median 50% for both, p = 0.97) between samples with prior negative and prior positive results. Prior negative results were also identified in 16/20 (80%) cases with non-V600 mutations, two of which harbored multiple BRAF alterations [K601E (4), D594A/G/N (4), S467L (2), L584F (2), G464V, G466V, G469V, E586K, N581I, L597Q, A589_T599insT]. Two of 2 (100%) cases with activating BRAF fusions also had prior negative BRAF results. Clinical outcomes for a subset of patients will be presented.

Conclusions: Despite approved companion diagnostics, significant variability exists in methods for BRAF testing in the clinical setting. Hybrid-capture based NGS identifies diverse activating mutations and fusions, including BRAF V600E, in a significant fraction of cases for which prior BRAF testing returned negative results. Given the proven clinical benefit in patients with BRAF alterations treated with match targeted therapies, hybrid-capture based NGS should be considered for patients with metastatic melanoma, particularly if other testing is negative.

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

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Disclosure: A. Wang, J.S. Ross, P.J. Stephens, S.M. Ali, A.B. Schrock, V.A. Miller: Employee with stock ownership in Foundation Medicine, Inc. All other authors have declared no conflicts of interest.

1235P Post-transcriptional regulation of immune checkpoint genes by mir-16 in melanoma

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Background: The complex interface between T lymphocytes and cancer ('the immunological synapse') comprises of both co-stimulatory and co-inhibitory proteins that modulate lymphocytes towards activation or anergy. 'Checkpoint inhibitors' have impressive activity in melanoma, but not all patients respond and drug resistance often develops. MiRNAs are master regulators of gene expression. Our aim is to study the regulation of the immunological synapse by miRNAs in melanoma.

Methods: Bioinformatic analyses of mRNAs and miRNA expression in 451 samples from the melanoma TCGA database was performed. Spearman rho correlation coefficients were calculated and survival analysis was performed using the Kaplan-Meier method. Direct mRNA targets of miRNAs were found using luciferase reporter assays, and mRNA/miRNA expression was assessed by qRT-PCR following either ectopic expression or depletion of specific miRNAs.

Results: Of 15 checkpoint mRNAs and 8 miRNAs examined, nine checkpoint mRNAs showed a highly statistically significant positive correlation to each other and, to a lesser extent, to mir-16. These results were fully corroborated in vitro. Mir-16 may potentially target the 3'UTR of 3 of these mRNAs. CD80 (B7.1) was found to a direct target of mir16 in vitro. Overexpression of mir-16 in melanoma cell lines led to downregulation of CD80, CD274 (PD-L1) and CD40, while downregulation of mir-16 increased the expression of these genes. Survival data from 163 stage III melanoma patients show that high levels of mir-16 and low levels of any of six checkpoint mRNAs (among them CD80) is significantly associated with poor prognosis.

Conclusions: Our results suggest that mir-16 and many checkpoint mRNAs are generally under a strict joint transcriptional regulation. The ability of mir-16 to decrease CD80 expression suggests that it serves as a key regulator of the immunological sample. We hypothesize that in vivo, an aberrantly high expression of mir-16 decreases the expression of the co-stimulatory checkpoint CD80 in melanoma and other checkpoint mRNAs, leading to immune evasion and compromised outcome. Further elucidation of both the transcriptional and post-transcriptional regulation of the immunological synapse may help point to novel targets and means for immune modulation.

Legal entity responsible for the study: Raya Leibowitz-Amit

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1236P Does melanoma or other skin cancers belong to the BRCA2 phenotype?

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Background: The *BRCA2* phenotype includes breast (BC) and ovarian cancer (OC) as well as, less frequently, prostate (PC), gastric (GC) and pancreatic cancer. The association with melanoma remains unclear, because previous studies were retrospective and included non- confirmed carriers. With this study we intend to determine the rate of melanoma and nonmelanoma skin cancers diagnoses in a consecutive prospective cohort of confirmed BRCA2 carriers.

Methods: Review of all skin cancer diagnoses in BRCA2 carriers under prospective surveillance.

Results: Four hundred and eighty six BRCA2 carriers (376 female, 110 male) belonging to 216 families were identified. The median age for genetic diagnosis was 48,3yrs with the BRCA2 c.156_157inAlu being the mutation most frequently observed (43,6%). Most carriers (359/486) had yearly full skin examinations. Although a majority of women (226/376) were cancer survivors (209 BC, 29 OC and 12 with breast/ovarian cancer), only 30/110 men had a previous cancer diagnosis (20 BC, 8 PC and 2 GCs). For a median follow up of 4 yrs, melanoma diagnoses were 3 in 2 female with bilateral BC. The patient with 2 melanomas had the first melanoma at 28yrs before BC diagnoses. Other skin cancers: 14 squamous cell carcinoma (SCC) (8 invasive, 6 in situ SCC) and 14 pts with basal cell carcinoma (BCC), 6 of which with multiple BCC. Four pts were diagnosed with actinic keratosis (AK). The rate for melanoma is 0,4% and for nonmelanoma skin cancers 5%. The rate for skin cancer in BRCA2 carriers with a previous cancer diagnosis is 2%. No statistical significance was found either for the association of skin cancer ($p = 0{,}221$) or melanoma ($p = 0{,}9$) with specific BRCA2 mutations.

Conclusions: The low rates of melanoma diagnosis in our prospective confirmed BRCA2 cohort, raises questions about the previously described association of melanoma and BRCA2 mutations. Also, no association was found between the Portuguese founder mutation and melanoma or other skin cancers. Although more follow up may be needed, there is insufficient evidence to warrant increased skin surveillance of BRCA2 carriers in the absence of standard skin cancer risk factors.

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Disclosure: All authors have declared no conflicts of interest.

1237P Resected malignant melanoma at high risk of recurrence in SEER-Medicare

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Background: While surgery remains a mainstay in the management of high-risk resectable malignant melanoma (MM), there is a high chance of recurrence. Utilization of approved adjuvant therapies (e.g. interferon α and ipilimumab) are limited by the common occurrence of debilitating side effects. The objective of our study was to describe characteristics of patients (pts) with resected MM at high risk of recurrence in the older US population.

Methods: A retrospective cohort study was undertaken using the Surveillance, Epidemiology, and End Results (SEER)-Medicare population-based linked database. The study population included pts with Stage IIC-IIIC surgically resected MM diagnosed between 2004 and 2011. Demographic and clinical characteristics, adjuvant therapies, including radiation (XRT) and/or systemic therapy (eg, interferon α, interleukin, pegylated interferon), and overall survival (OS) were evaluated.

Results: We identified 1016 pts; the mean age was 75.2 years (interquartile range [IQR], 72–82) and 66.2% were males. The majority of pts had Stage IIC-IIIB disease at diagnosis (Cohort 1; $n = 877$ [86.3%]); the remainder had stage IIIC disease (Cohort 2; $n = 139$ [13.7%]). Adjuvant therapy was utilized in 27.3% ($n = 239$) and 43.2% ($n = 60$) of pts in Cohorts 1 and 2, respectively, and consisted of XRT in 74% and 78% of pts, systemic therapy in 16% and 10% of pts (with interferon α representing 98.6% of systemic therapies), and a combination of XRT and systemic therapy in 10% and 12% of pts. OS differed between cohorts, with a median of 32.3 months (IQR, 17.9–53.3) for Cohort 1 and 19.8 months (IQR, 11.5–36.2) for Cohort 2. Landmark OS at 5 years was 20.8% for Cohort 1 and 12.2% for Cohort 2.

Conclusions: Among pts with resected MM at high risk of recurrence in the older US population, utilization of adjuvant therapy and OS varied based on disease stage at diagnosis. Pts with Stage IIIC disease were exposed to more medical interventions; however, use of highly toxic systemic therapy available during the study period was limited in both cohorts. As more therapies for the adjuvant setting are being developed, the evaluation of clinical and demographic characteristics may help tailor treatment regimens.

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

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Disclosure: N. Sadetsky, A. Hernandez, D. Colburn: Employee, Genentech, Inc. G. Goodman: Employee, Genentech, Inc.; owns stock in Roche. All other authors have declared no conflicts of interest.

1238P Independent prognostic impact of lympho-vascular invasion in cutaneous melanoma patients with sentinel lymph node biopsy

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Background: Incidence of cutaneous melanoma (CM) is increasing worldwide. The primary treatment of CM is surgery. Prognosis is determined by characteristics of the lesion such as depth of invasion, ulceration and sentinel lymph node (SLN) status. The aim of this study was to analyze the prognostic impact of lympho-vascular invasion (LVI) in CM patients (pts) undergoing SLN biopsy since LVI has not been established as a clear prognostic factor in the current AJCC 8th ed. cancer staging system.

Methods: Retrospective, descriptive and observational analytical study. We used the institutional database of pts with diagnosis of CM, submitted to SLN biopsy between November 1994 and August 2016. The association between pathological characteristics and SLN were analyzed using Chi2 and logistic regression model. Kaplan Meier and Log rank were used for disease free survival (DFS) analysis.

Results: 385 pts with a diagnosis of CM were analyzed. Median follow-up 45.2 months (IQR: 15.66-91.77). Median age: 52 years (IQR 42-65). SLN+: 47/384 (12.2%). Evaluated prognostic factors: Breslow (Br) 1.5 mm md (IQR 1-2.67), ulceration + 94/385 (24.4%), LVI + 32/144 (22.2%). Relapse 86/367 (23.4%). In the univariate analysis we found association between relapse and the following factors: LVI + (OR: 2.97, $p = 0.0125$), SLN + (OR: 3.97, $p < 0.01$), Br ≥ 1mm (OR: 4.13, $p = 0.01$) and ulceration + (OR: 2.08, $p < 0.01$). There was no association with age and sex. In the multivariate analysis LVI + (OR: 2.47, $p = 0.049$) and SLN + (OR: 3.91, $p = 0.048$)

were associated with relapse, whereas neither Br ≥ 1 mm, sex nor ulceration were associated with relapses. 5-year-DFS was higher in SLN - (79.3% vs 56.1%, p < 0.01), LVI - (80.7% vs 57.9%, p 0.019), Br < 1 mm (89.5% vs 71%, p < 0.01) and ulceration - (80.4% vs 59.7%, p < 0.01).

Conclusions: In our retrospective series, after a long period of follow-up, the presence of LVI as an independent factor was associated with relapse and DFS. Within CM pts the best candidate for adjuvant therapy is yet to be defined, LVI + as a prognostic factor should be validated in prospective trials in this scenario.

Legal entity responsible for the study: Instituto Alexander Fleming

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Disclosure: All authors have declared no conflicts of interest.

1239P Validating prognostic models in metastatic uveal melanoma (MUM), an international rare cancers initiative

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Background: We validated 2 models (the 7thAmerican joint committee on cancer (AJCC) and the Helsinki university central hospital (HUCH) staging) and 1 nomogram; the Padova-Mayo (PMN), for progression free (PFS) and overall survival (OS) using patient (pt) level data from the PUMMA meta-analysis.

Methods: 29 prospective trials' (1988-2015) pt data was analysed. Models were validated with cox regression analysis for survival in months (m). Concordance index (CCI) was used to test predictive value.

Results: Comparable data was available for 463 pt; see table for variables used in each system. Models were prognostic differentiating into M1a, M1b and M1c groups. Median PFS for AJCC was 4m for M1a, 3 for M1b and 2 for M1c. Median PFS for HUCH was 3.5m for M1a, 2.5 for M1b and 1 for M1c. CCI for PFS using AJCC was 0.69 (SE 0.02, 95%CI 0.65-0.73), for HUCH it was 0.79 (SE 0.02, 95%CI 0.74-0.83). Median OS for AJCC was 15m for M1a, 9 for M1b and 5 for M1c. Median OS for HUCH was 13m for M1a, 6 for M1b and 2 for M1c. CCI for OS for AJCC was 0.69 (SE 0.02, 95%CI 0.65-0.73). For HUCH it was 0.79 (SE 0.02, 95%CI 0.74-0.83). Using ECOG and LDH (available variables used in PMN) median PFS was 4m (95% CI 4-5) for normal LDH and ECOG 0, 7 (3-9) for normal LDH and ECOG > 0, 2.6 (2-3) for elevated LDH and ECOG 0 and 2.5 (2-3) for elevated LDH and ECOG > 0. Corresponding median OS was 17m (95%CI 15-18), 12.7 (95%CI 10-19), 7.4 (95%CI 6.3-8.9) and 5.3 (95%CI 3.8-6.1). CCI were PFS 0.72 (SE 0.02, 95% CI 0.69-0.75), OS 0.73 (SE 0.02, 95% CI 0.7-0.76).

Conclusions: Prognostic models in MUM remain imprecise in an externally validated dataset. Further validation is needed to find clinical utility

Legal entity responsible for the study: Princess Margaret Cancer Centre

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Disclosure: L. Khoja: Employed by Astrazeneca plc. All other authors have declared no conflicts of interest.

1240P Impact of an active surveillance programme on outcome of patients (pts) with uveal melanoma (UM) after primary curative therapy (PTx): results of a single-institution experience

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Background: About 30% of pts with UM develop metastatic disease (MUM) despite PTx. Liver is by far the commonest site of metastases. MUM has poor prognosis and no systemic treatment (STx) has been proven to improve overall survival (OS). However, the role of active surveillance for metastatic disease 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 initial diagnosis of UM and then 6-monthly liver imaging (CT triple-phase or 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 166 pts registered between April 2009 and April 2017, 36 (22%) developed MUM: 14 pts relapsed <2 yrs, 17 between 2 and 5 yrs, 5 >5 yrs from PTx. MUM pts characteristics: males 19 (53%); median age 58 (range 34-85); median tumour thickness at diagnosis 9mm (2-22); sites of metastases: liver only 13 (36%), liver + other sites 21 (58%), extra-hepatic only 2 (6%). Relapses were asymptomatic and detected on surveillance imaging in 29 (80%) pts. Nine pts (7 detected from surveillance) underwent primary hepatic metastasectomy (HM), 27 (75%) pts were non-resectable (NR) and underwent STx (n = 18), locoregional Tx (n = 4), best supportive care (n = 5). Overall, 29/36 MUM pts received immunotherapy with either ipilimumab or nivolumab/pembrolizumab. At a median FU of 36.5 mos (1-103), 27 pts have died and the median OS is 16.6 mos (95%CI: 7.8-25.3). Both PFS and OS were statistically significantly longer for HM pts compared to NR pts (PFS: 10.8 vs 4.4mos, $p = 0.01$/OS: 24.9 vs 13.4mos, $p = 0.04$). Eight out of 9 pts developed further disease relapse after HM.

Conclusions: Our data indicate that active surveillance after PTx of UM can allow detection of asymptomatic potentially resectable liver metastases, especially in pts with

Table: 1239P

Variable (n = 463) (n (%), median, range)		7thAJCC	HUCH	PMN
ECOG	0			296 (64) 156 (34) 11 (2)
	1			
	> 2			
Diameter in cm of largest metastasis	< 3 cm	1.9 (0-2.9)		
	3-8 cm	4.4 (3-8)		
	> 8 cm	10.8 (8.1-22.5)		
Diameter of largest liver lesion			3.8 (0-22.5)	
% liver involvement	< 20 20-50 > 50 Missing			3 (0-65) 5 (1) 3 (1) 452 (98)
LDH				344 (39-8198)
ALP			89 (24-1178)	
Disease free interval				Missing
OS (%, 95% CI)				
M1a	6	89 (83-93)	84 (80-88)	
	12	60 (52-68)	55 (49-60)	
	24	25 (18-33)	22 (18-27)	
M1b	6	68 (62-74)	48 (39-57)	
	12	38 (31-44)	17 (11-24)	
	24	14 (94-19)	5 (2-1)	
M1c	6	45 (33-57)	8 (0-29)	
	12	19 (10-29)	0	
	24	78 (27-17)	0	

high risk UM (i.e. tumour thickness >5mm). Although durable remission after HM is rare PFS and OS may be significantly prolonged.

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Disclosure: All authors have declared no conflicts of interest.

1241P Impact of duration of response (DOR) on overall survival (OS) in patients with metastatic melanoma treated with dacarbazine (DTIC), vemurafenib (V), or cobimetinib plus vemurafenib (C+V): a pooled analysis

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Background: Evaluation of treatment efficacy in oncology using OS is confounded by survival benefit from post-progression treatment. We pooled data from the BRIM-2, -3, -7, and coBRIM studies (BRAF inhibitor–naive patients with $BRAF^{V600}$-mutated metastatic melanoma) to evaluate whether DOR could be a surrogate for OS.

Methods: Time-dependent Cox proportional hazards regression was used to model the association of DOR (interval from date of first RECIST response to progressive disease [PD] or death) with OS. The risk of death for DORs of 1–10 months (in 1-month increments) was evaluated. Patients with best response of stable disease or PD [nonresponders (NR)] were assigned a DOR of zero. Models were adjusted for time-fixed baseline covariates (ECOG status, demographics, disease covariates, and first-line treatment), and time-dependent covariates (DOR and post-progression treatment [immunotherapy, targeted therapy, or other]).

Results: This analysis included 1365 patients (DTIC = 338; V = 717; C+V = 310). Objective response was 47.5% for the overall population and 11.5%, 53.6%, and 72.9% for the DTIC, V, and C+V cohorts, respectively. Median DOR was 9.3 months in the overall population and 6.4, 7.6, and 14.6 months in the DTIC, V, and C + V cohorts, respectively. Cox proportional hazards adjusted for time-dependent covariates showed a significant and progressive reduction in the risk of death with increasing DOR vs NR. The absolute risk of death decreased by a mean of ≈6.3–7.7% per month increase in DOR in the overall population and across treatment cohorts (Table). Sensitivity analyses in responders only showed similar results.

Conclusions: These exploratory analyses suggest that DOR is independently associated with OS outcomes regardless of treatment and merits further exploration as a surrogate endpoint to assess long-term treatment benefit.

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1242P Neutrophil to Lymphocyte Ratio (NLR) as an independent prognostic measure in patients receiving targeted therapy or immunotherapy for stage IV melanoma

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Background: Treatment of metastatic melanoma has rapidly evolved with the introduction of targeted and immunotherapies in recent years. An elevated NLR (neutrophil-lymphocyte ratio) has been shown to be an independent marker of poor prognosis in malignancies including melanoma. Here we present an updated survival analysis demonstrating the utility of NLR as a marker of prognosis in patients with metastatic melanoma receiving targeted and immunotherapy.

Methods: We identified patients with stage 4 melanoma who received systemic therapy with targeted therapy (BRAF +/- MEK inhibitor) or immunotherapy (Anti-CTLA-4 or Anti-PD-1) at our institution. Patients not receiving any systemic therapy were excluded. We retrospectively reviewed all medical records collecting data on baseline demographics, prognostic factors (stage, LDH, CNS and Liver metastases), treatments received, pre-treatment NLR and outcomes. Overall survival (OS) and Progression-free survival (PFS) were measured from date of first dose received.

Results: 174 patients were treated between August 2010 to November 2016, 74 received targeting therapy and 100 receiving immunotherapy. Median follow up was 10 months. At time of interim analysis median OS for patients with NLR < 5 was 11.7 months compared to 4.8 months in NLR >5 (HR 0.45, 95% C.I. 0.31-0.67, p = 0.00007), this was seen in patients treated with both targeted therapies (HR 0.48, p = 0.012) and immunotherapies (HR 0.40, p = 0.0009). Median PFS was also longer in patients with NLR <5 4.8 vs. 3.6 months (HR 0.65, p = 0.02). Multivariate analysis including age, sex, M stage, baseline LDH and CNS/Liver metastases, demonstrated NLR was the strongest predictor of OS (HR 0.39 95% C.I. 0.25-0.60, p = 0.00002).

Conclusions: NLR >5 is a strong independent predictor of poor outcome in patients with metastatic melanoma regardless of targeted or immunotherapy. We hypothesis that at final data lock in July 2017 this association will remain strong given it was a clear predictor of outcome at the time of interim analysis. NLR may assist selection of initial therapy, for example, a favourable ratio may indicate suitability for single agent rather than doublet immunotherapy with its greater toxicity profile.

Legal entity responsible for the study: Alfred Health

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Disclosure: All authors have declared no conflicts of interest.

Table: 1241P Hazard of death by duration in response (excluding time-dependent PD variables)

Patient cohort	DOR of 1 month HR (95% CI)	DOR of 10 months HR (95% CI)	Mean per month HR decrease	Range of HR decrease	P-value[a]
All patients	0.85 (0.82–0.87)	0.19 (0.14–0.25)	0.073	0.034–0.130	<0.0001
V	0.80 (0.77–0.84)	0.11 (0.07–0.18)	0.077	0.028–0.157	<0.0001
C+V	0.89 (0.86–0.93)	0.33 (0.23–0.46)	0.063	0.039–0.095	<0.0001
DTIC	0.81 (0.71–0.92)	0.12 (0.03–0.45)	0.076	0.029–0.154	0.0016
All responders[b]	0.88 (0.85–0.90)	0.27 (0.21–0.35)	0.068	0.038–0.108	<0.0001
V	0.84 (0.80–0.88)	0.17 (0.11–0.27)	0.074	0.033–0.135	<0.0001
C+V	0.91 (0.88–0.94)	0.37 (0.27–0.51)	0.059	0.039–0.086	<0.0001
DTIC	0.87 (0.78–0.97)	0.26 (0.09–0.77)	0.069	0.037–0.111	0.0148

HR, hazard ratio.

[a]Association of DOR with risk of death.

[b]Patients with complete or partial response.

1243P The prognostic significance of distant metastasis free interval (DMFI) in BRAF mutant advanced melanoma patients treated with first line targeted therapy

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Background: Prognostic models are investigated for advanced melanoma patients treated with targeted therapy. This study aims to identify the relationship between DMFI and outcome of 1st line targeted therapy in BRAF mutant (BRAFmut) patients.

Methods: BRAFmut patients identified from 2 referral centres were assigned to 3 prognostic groups: A (PS 0, Metastatic sites $\leq$3, LDH normal, CNS not involved), B (PS 1, Metastatic sites $\leq$3, LDH >1-2ULN, CNS not involved), C (PS 2, Metastatic sites >3, LDH $\geq$2ULN, CNS involved or not). Factors analysed: Distant Metastasis Free Interval (DMFI from primary melanoma to 1st distant metastasis), Post Relapse Progression Free Survival (PRPFS post relapse to BRAFi), Post Relapse Survival (PRS), number of metastatic sites, LDH, CNS involvement, PS. Univariate and multivariate Cox regression analysis was used adjusted with the 3 prognostic groups. Statistical analysis with STATA/SE V13.0.

Results: From 380 advanced melanoma patients, 161 BRAFmut patients received 1st line BRAFi only (101) or BRAFi+MEKi (60). Patients relapsed from primary at a median DMFI 12 months (range 0-185) and were included in the 3 prognostic groups (Group A 27, Group B 72, Group C 56). To study DMFI significance, we defined 2 patient groups according to DMFI: DMFI <24 months Group 1, DMFI $\geq$24 months Group 2. Median PRPFS was 5 months for Group 1 and 8 months for Group 2 with statistically significant difference (HR = 1.45, 95%CI 1.01-2.09, p = 0.046). In multivariate analysis, DMFI also emerged as independent prognostic factor (HR 1.44, 95% CI 0.99-2.10, p = 0.059). Prognostic Group (C vs A), number of metastatic sites ($\geq$3 vs < 3), PS (0 vs 1-2), and LDH (>2ULN vs normal) were confirmed as independent prognostic factors for PRPFS and PRS. ROC analysis on progression showed best DMFI cut-off at 26 months (9 vs 5), HR 1.6 (95%CI 1.10-2.33), p = 0.014 [sen 46.2%, spec 69.6%]. No difference in median PRS between the 2 groups (14 vs 16 months, p = 0.517), possibly reflecting effect of therapies after BRAFi.

Conclusions: Patients with BRAFmut advanced melanoma and DMFI <2 years have significantly worse post relapse PFS after 1st line targeted therapy. Our results indicate DMFI as an independent prognostic factor for BRAFmut patients.

Legal entity responsible for the study: A' Oncology Dept, Metropolitan Hospital

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1244P Hospitalization Rates in COLUMBUS Part 1: A Phase 3 Trial of Encorafenib (ENCO) Plus Binimetinib (BINI) Versus Vemurafenib (VEM) or ENCO in BRAF-Mutant Melanoma

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Background: Part 1 of the COLUMBUS study demonstrated that the BRAF inhibitor ENCO 450 mg once daily (QD) + the MEK inhibitor BINI 45 mg twice daily (BID; COMBO450) improved progression-free survival vs VEM 960 mg BID alone and ENCO 300 mg QD (ENCO300) alone in patients (pts) with advanced *BRAF* V600–mutant melanoma. Tolerability of COMBO450 was favorable compared with VEM or ENCO300. Here we evaluate resource utilization based on hospitalization data (ClinicalTrials.gov, NCT01909453; EudraCT, 2013-001176-38).

Methods: Pts were randomized 1:1:1 to receive COMBO450, VEM, or ENCO300. Efficacy endpoints, including the number of pts hospitalized and number of hospitalizations, were described. Time to first occurrence of hospitalization was assessed by the Kaplan-Meier method. Hospitalization endpoints were adjusted per 100 pt-months (pt-mo) of exposure to study drug.

Results: Among 577 pts, 192 were randomized to COMBO450, 191 were randomized to VEM, and 194 were randomized ENCO300. Exposure-adjusted hospitalization rates (per 100 pt-mo) were 3.5% in the COMBO450 arm compared with 4.3% and 6.2% in the ENCO300 and VEM arms, respectively. Exposure-adjusted mean duration of hospitalization per 100 pt-mo was 32.5, 38.2, and 53.7 days in the COMBO450, ENCO300, and VEM arms, respectively. Median (95% CI) time to first hospitalization for pts with $\geq$1 event was 5.1 (2.6–6.1) mo in the COMBO450 arm compared with 2.8 (0.8–4.2) and 2.8 (2.0–3.8) mo in the ENCO300 and VEM arms, respectively.

Conclusions: Resource utilization, as determined by hospitalization data in COLUMBUS Part 1, was lower with COMBO450 compared with VEM or ENCO300 monotherapy.

Clinical trial identification: Trial protocol number, CMEK162B2301 (release date, July 13, 2015)

Legal entity responsible for the study: Array BioPharma Inc.

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1245P Quality-of-life (QoL) in COLUMBUS part 1: A phase 3 trial of encorafenib (ENCO) plus binimetinib (BINI) versus vemurafenib (VEM) or ENCO in braf-mutant melanoma

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Background: In COLUMBUS Part 1, the BRAF inhibitor ENCO 450 mg once daily (QD) + the mitogen-activated protein kinase kinase (MEK) inhibitor BINI 45 mg twice daily (BID; COMBO450) improved progression-free survival vs VEM 960 mg BID alone and ENCO 300 mg QD (ENCO300) alone in patients (pts) with advanced *BRAF* V600-mutant melanoma. Tolerability of COMBO450 was favorable compared with VEM or ENCO300. Here we compare patient-reported health-related QoL between the treatment arms.

Methods: Pts were randomized 1:1:1 to receive COMBO450, VEM, or ENCO300. Patient-reported health-related QoL was assessed by 2 validated instruments, the Functional Assessment of Cancer Therapy–Melanoma (FACT-M) questionnaire and the European Organization for Research and Treatment of Cancer's Quality of Life Questionnaire–Core 30 (EORTC QLQ-C30). Higher scores represent better QoL on both instruments. A mixed-effect model for repeated measures was used to compare the change from baseline (BL) in the domain scores over time.

Results: Among 577 pts, 192 were randomized to COMBO450, 191 were randomized to VEM, and 194 were randomized ENCO300. Compliance of pts completing the FACT-M and EORTC QLQ-C30 questionnaires was equivalent; approximately 80%–90% of pts still at risk completed the assessment from BL through cycle 25. Mean BL FACT-M scores were similar between arms (52.39, 52.01, and 52.84 in the COMBO450, VEM, and ENCO300 arms, respectively). FACT-M subscale change over time indicated that COMB450 was associated with an estimated 2.98 point higher post-BL score vs VEM (95% confidence interval [CI] 1.34–4.63) and a 4.01 pt higher post-BL score vs ENCO300 (95% CI 2.47–5.54). Mean EORTC QLQ-C30 scores at BL were 66.72, 64.74, and 66.10 with COMBO450, VEM, and ENCO300, respectively. Evaluation of change over time found that COMBO450 was associated with an estimated 5.25 point higher post-BL score vs VEM (95% CI 1.21–9.29) and an 8.32 higher post-BL score vs ENCO300 (95% CI 4.54–12.11).

Conclusions: Patient-reported health-related QoL was rated consistently and significantly better with COMBO450 vs VEM or ENCO monotherapy.

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1246P Loss of USP28 drives resistance to BRAF targeted therapy in melanoma

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Background: Metastatic melanoma is a lethal malignancy leading to an estimated 65,000 deaths annually worldwide. The serine threonine kinase BRAF is mutated in 40-60% of all melanoma patients frequently at a single hotspot BRAF V600E, which results in hyperactivation of MAPK pathway. RAF kinase inhibitors are clinically active in patients with BRAF (V600E) mutant melanoma. However, rarely do tumours regress completely with the majority of responses being partial and short-lived. Several mechanisms of resistance to RAF inhibitors have been suggested in melanoma. In addition to somatic genomic alterations recent studies have revealed the importance of ubiquitination in the role of MAPK signaling. Yet very little is known about the deubiquitinating enzymes that counteract ubiquitination mediated functions. Our study identified loss of deubiquitinating enzyme, USP28 as a novel mechanism of resistance to vemurafenib in BRAF mutant melanoma.

Methods: A genome wide shRNA screen targeting all known deubiquitinating enzymes was performed and level of phosphorylated ERK as the representative of MAPK pathway was assessed by western blotting. Significant hits of the screen were validated and mechanism of action in regulation of MAPK pathway and resistance to MAPK inhibitors in melanoma has been investigated.

Results: Using a functional RNAi screen targeting all known human deubiquitinating enzymes, we identified USP28 as a critical regulator of MAPK pathway. It is known that USP28 binds to and stabilizes the E3 ligase substrate recognition subunit, FBW7 to regulate stability of various proteins. We showed that the USP28/FBW7 complex directly ubiquitinates BRAF and targets BRAF for ubiquitin mediated degradation. Importantly, TCGA datasets indicates that USP28 is deleted in 9% of melanoma patients. Using Kaplan-Meier analysis, we showed that loss of USP28 confers poorer overall survival in melanoma patients. We showed that loss of USP28 enhances MAPK activity through the stabilization of BRAF. Our results revealed the Loss of USP28 drives resistance to RAF inhibitor therapy in BRAF(V600E) tumors both *in vitro* and *in vivo*.

Conclusions: Taken together we showed loss of USP28 as a potential biomarker for MAPK activation and vemurafenib resistance in BRAF 600E mutant melanoma.

Legal entity responsible for the study: National University of Singapore

Funding: Cancer Science Institute of Singapore, National University of Singapore

Disclosure: All authors have declared no conflicts of interest.

1247P Patterns of progression in metastatic melanoma patients treated with Braf and Mek inhibitors: an Italian Melanoma Intergroup (IMI) study

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Background: Patterns of progression after BRAF+MEK inhibitors (I) could help clinicians in understanding the best treatment strategy among the multiple available

options in the BRAFv600 melanoma setting. We analysed outcomes in patients (pts) treated with BRAF+MEK I to characterize pts with rapid progression.

Methods: In this multicenter retrospective analisis, 164 consecutive pts affected by BRAFv600 metastatic melanoma and treated with BRAF+MEK I from February 2012 to April 2017 were included.

Results: Overall, 164 patients were enrolled. Baseline LDH was elevated in 68 (41%) pts, baseline number of metastatic organs were 1, 2, 3 and more in 52 (32%), 52 (32%), 29 (18%), and 32 (19%) pts. BRAF+MEK I administered were dabrafenib+trametinib in 151 pts and vemurafenib+cobimetinib in 13 pts, and they were administered in first line in 129 (79%) pts. Best response was CR, PR, SD and PD in 27 (16%), 87 (53%), 17 (10%) and 27 (16%) pts. On cutoff date, progression was observed in 104 (63%) pts; 60 (37%) pts still on treatment. mPFS was 9,83 (1-54,7+) months: significant difference in PFS was showed in pts with normal baseline LDH or high LDH (13.2 vs 6.3 months, $p < 0.0001$), and in pts with number of metastatic organs lower or higher then 2 (13,4 vs 7 months, $p < 0.0001$). mOS was 18.3(1-62,5+) months: significant difference in OS was showed in pts with normal baseline LDH or high LDH had (24,7 vs 10 months, $p < 0.0006$), and in pts with number of metastatic organs lower or higher then 2 (25.9 vs 10 months, $p < 0.0003$). Among 104 progressed pts, 72 (69%) pts died, mOS after progression was 2,5 months (0,5-42+ months); Subsequent treatments were administered in 44 (42%) pts. Duration of response (DR) was defined as time from BRAF+MEK I best response to progression of disease. Significant difference in OS after BRAF+MEK I progression was observed in pts with DR < 6 months(77 pts -74%) or > 6 months (27 pts - 26%) (2 vs 8,3 months, $p < 0.0023$) and in pts with number of metastatic organs after progression lower or higher then 3 (4,5 vs 2 months, $p < 0.022$).

Conclusions: DR and extension of progression during BRAF+MEK I are factors that can be useful to identify pts with lower OS after progression, in addiction to known parameters like LDH and baseline number of metastatic organs.

Legal entity responsible for the study: IMI

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1248P Tumor-stroma interactions as a determinant of drug resistance in BRAF-mut melanoma

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Background: In BRAF-mut melanoma combined BRAF/MEK inhibition increases survival; however, pharmacological effects on the genetically "normal" tumor microenvironment (i.e. paradox MAPK activation) may set the stage for the development of drug resistance.

Methods: GFP-labeled cutaneous fibroblasts (HFF) were co-cultured with melanoma cells, in the presence or absence of direct cell-cell contact, and response to Dabrafenib (D) and Trametinib (T), alone or combined, was monitored over time. SEMA6A and AXL were preliminarily evaluated as potential mediators of such interactions.

Results: HFF significantly protected (60-100% protection at the lowest two drug concentrations) BRAF-mut M14 melanoma cells from the growth inhibitory activity of D and T, alone or combined; however, combined D+T at the highest concentrations overcame stroma-mediated protection and eliminated both cell populations. Thus, combined BRAF/MEK inhibition resulted in strongly synergistic interactions, as compared to single agent treatments, only under co-culture conditions (CI 0.6 and 0.2 for M14 and HFF cells, respectively). Protective melanoma/stroma interactions were mediated by direct cell-cell contact, as co-cultures in trans-well Boyden chambers or isolated cultures using conditioned medium (HFF-conditioned medium for M14; M14-conditioned medium for HFF), did not affect pharmacological response. As SEMA6A expression is tightly controlled by MAPK and AXL mediates resistance to MAPK inhibition in melanoma, we assessed their potential as mediators of stroma-mediated melanoma protection: interestingly, SEMA6A and AXL expression in a panel of melanoma cell lines were inversely correlated; moreover, in cell lines derived by primary and cutaneous metastases of the same patient, AXL expression was upregulated at the mRNA and protein level in cells derived from metastatic lesions.

Conclusions: Tumor-stroma interactions protect BRAF-mut melanoma from MAPK inhibition; such functional protection is mediated by cell-cell contact. SEMA6A and AXL are possible mediators of this interaction and their reciprocal relationships are being studied in melanoma cell line models and clinical series.

Legal entity responsible for the study: Regina Elena Cancer Institute- San Gallicano Dermatologic Institute

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1249P Extended survival analysis of ipilimumab for the treatment of advanced malignant melanoma in pretreated patients: Five-year long-term follow-up of the South African expanded access program

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Background: Ipilimumab is a human monoclonal IgG1 antibody against CTLA-4 that has been shown to prolong the overall survival of patients with advanced pretreated melanoma. In 2015, a retrospective, multi-centre, non-interventional analysis was performed on data collected from the ipilimumab expanded access programme in South Africa, with last follow-up date (or death) in December 2014. The current study extends this analysis by follow-up on the long-term survival of pre-treated metastatic patients up to September 2016.

Methods: Follow-up questions were sent to participating investigators, who had patients who were still alive (29) or for whom it was not known whether they were still alive (11) following the last ipilimumab infusion. Investigators had to confirm whether patients were still alive, the date of death or last contact, clinical response at last contact, and whether the patient was still responding to ipilimumab.

Results: Of the 108 patients, 84 (78%) had cutaneous melanoma and 24 patients (22%) had non-cutaneous melanoma, including uveal, mucosal, and melanoma of unknown primary. Twenty patients previously received two or more lines of treatment for metastatic melanoma. The median age was 59 years (range 27 – 86) and there were 73 (68%) males and 35 (32%) females. Baseline ECOG PS was 0 in 33%, PS 1 in 58% and PS 2 in 6% of patients. The longest follow-up time available was 5.4 years. The median OS was 9.36 months (95% CI 7.48 – 11.84). One-year survival was 39% (95% CI 29% - 48%), 2-year survival was 22% (95% CI 15% - 30%), 3-year survival was 19% (95% CI 12% - 27%), 4- and 5-year survival was 15% (95% CI 8% - 21%). In the group of cutaneous melanoma patients, the 4- and 5-year survival was 17% (95% CI 9% - 25%) while in the non-cutaneous group the 4- and 5-year survival was 6% (95% CI 0% - 16%).

Conclusions: Ipilimumab at a dose of 3mg/kg is an effective treatment for patients with pre-treated advanced (unresectable or metastatic) melanoma and is associated with durable remissions and long-term survival.

Clinical trial identification: Protocol number: CA184-515 Ethics approval extended on protocol REC 2/21/05/14

Legal entity responsible for the study: Dr Bernardo L Rapoport

Funding: Investigator Sponsored Research (ISR) trough Bristol-Myers Squibb

Disclosure: H. Duvenhage: Head of Medical at Bristol-Myers Squibb All other authors have declared no conflicts of interest.

1250P Real-world use of ipilimumab and nivolumab monotherapy or in combination in patients with advanced melanoma: results from a retrospective chart review

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Background: The advanced melanoma treatment landscape has significantly changed with approval of ipilimumab (IPI) and nivolumab (NIVO). This analysis aimed to describe real-world characteristics and treatment patterns of patients (pts) prescribed IPI, NIVO, or NIVO+IPI.

Methods: This interim analysis of an observational, retrospective, multisite study collected data for US pts diagnosed with unresectable or metastatic melanoma who received IPI, NIVO, or NIVO+IPI (index) between January 2015 and May 2016. Demographics and treatment patterns were abstracted from medical records through most recent visit (≥6 months). Data were descriptively reported.

Results: Of 115 pts from 20 sites in the USA, 43 received IPI (mean±SD age 61.5±11.3 years, 51.2% female, 86.0% ECOG PS ≤ 1), 41 NIVO (age 65.9±13.7 years, 48.8% female, 90.3% ECOG PS ≤ 1), and 31 NIVO+IPI (age 57.1±11.3 years, 48.4% female, 100% ECOG PS ≤ 1). Tests for BRAF and PD-L1 were conducted in 98.3% and 39.1% of pts, respectively; 14.3%, 6.7%, and 12.2% of tested IPI, NIVO, and NIVO+IPI patients had a BRAF mutation, and 60%, 50%, and 79.0% of IPI, NIVO, and NIVO+IPI patients had a positive PD-L1 status. The index treatment was first line for 98.3% of pts; mean±SD days from advanced diagnosis to treatment initiation was 21.5±16.1 days for IPI, 55.1±68.6 for NIVO, and 41.5±68.6 for NIVO+IPI. The most common rationales for treatment initiation across treatments were improved efficacy (73.9%) and documented survival benefit (44.4%). Dose delays occurred in 9.3% of IPI pts (mean delay 12.7 days) and 6.5% of NIVO pts (mean delay 45 days); no NIVO+IPI pts had dose delays. At 6 months, 16% of pts remained on IPI, 85% remained on NIVO,

and 71% remained on the NIVO portion of the NIVO+IPI regimen. Permanent discontinuation of treatment prior to completing planned courses of therapy was relatively infrequent (IPI: 16%, NIVO: 26%, NIVO+IPI: 19%), possibly reflecting improved experience in toxicity assessment and management.

Conclusions: Within this real-world cohort, a minority of pts discontinued NIVO or NIVO+IPI by 6 months. This research sheds light on current treatment patterns for IPI, NIVO, and their combination.

Clinical trial identification: CA209-983

Legal entity responsible for the study: Bristol-Myers Squibb

Funding: Bristol-Myers Squibb

Disclosure: A. Tarhini: Served as a consultant or advisor for Bristol-Myers Squibb; received institutional research funding from Amgen, Bristol-Myers Squibb, Incyte, MSD, Novartis, and Prometheus Laboratories. C. Macahilig: Employed by Medical Data Analytics, where she provides study design and data collection. C. Atzinger: Received personal fees from Bristol-Myers Squibb; employee of Pharmerit International. K. Gupte-Singh: Employee of Bristol-Myers Squibb and has stock/ownership in Bristol-Myers Squib. C. Solem: Institution received consulting fees from Bristol-Myers Squibb to conduct this research. S. Rao: Employed of Bristol-Myers Squibb and has stock/ownership in Bristol-Myers Squibb.

1251P Baseline neutrophil-to-lymphocyte ratio and its values monitored over time is associated with outcome of metastatic melanoma patients treated with immunotherapy

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Background: Neutrophil-to-lymphocyte ratio (N/L) was shown to be prognostic in several solid malignancies. There are limited data about changes of N/L ratios during immunotherapy. The aim of the study was to asses a clinical value of this ratio and its association with tumour response in patients with advanced melanoma.

Methods: Between June 2011 and March 2017, 308 patients with metastatic/unresectable melanoma were included to the analysis. Patients age was 58.4±17.3 years (mean), 43 cases had brain metastases. *BRAF* mutation was present in 107 cases, and 98 patients with positive mutation received targeted therapies with BRAF+/- MEK followed by ipilumumab and/or anti-PD1 therapy. Patients with *BRAF* negative mutation received immunotherapy (pembrolizumab or nivolumab with/without ipilimumab). In all patients the N/L ratio was assessed at the baseline and monitored during treatment until disease progression or last observation. The cut off for ratio N/L was set at 3. Logistic GEE and Kaplan-Meier survival probability estimation were used for analysis.

Results: N/L ratio $\geq$3 at baseline was significantly associated with poorer overall survival (OS) ($p < 0.001$ in log-rank test). Median overall survival time was 25.8 months (95%CI 20.4-31.2) for N/L ratio <3 vs. 14.0 months (95%CI 10.7-17.3) for N/L ratio $\geq$3. In repeated measurements analysis, increased N/L ratio was significantly associated the confirmed disease progression, both in univariate random effect model ($p < 0.001$) and multivariate model adjusted for age, gender, presence of *BRAF* mutation and LDH>URL ($p < 0.001$). N/L ratio in all 6 patient who had pseudo-progression on immunotherapy was not elevated over time.

Conclusions: Our results confirm the usefulness of N/L ratio as a prognostic and predictive marker in patients with metastatic melanoma, and monitoring of the N/L ratio over immunotherapy may be helpful for assessment of the disease progression, response, as well as pseudoprogression, thus likely contributes to an optimization of treatment and resource allocation in patients with metastatic melanoma.

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

Funding: None

Disclosure: B. Cybulska-Stopa, H. Koseła-Paterczyk: Personal fees for lectures from Novartis, Roche, Bristol-Myers Squibb, MSD. K. Kozak: Personal fees for lectures from Novartis, Roche, Bristol-Myers Squibb and MSD. P. Rutkowski: Reports personal fees from Novartis, Bristol-Myers Squibb, Roche, MSD, GSK, Amgen - lecture honoraria and membership of Advisory outside the submitted work. All other authors have declared no conflicts of interest.

1252P Early safety from phase 1b/3, multicenter, open-label, randomized trial of talimogene laherparepvec (T-VEC) + pembrolizumab (pembro) for recurrent or metastatic squamous cell carcinoma of the head and neck (R/M SCCHN): MASTERKEY-232

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Background: T-VEC is the first FDA-approved oncolytic immunotherapy designed to activate antitumor immune responses. Pembro is a mAb against human programmed death receptor-1 that can stimulate inactivated anticancer T cells and is approved for the treatment (tx) of SCCHN. This combination of agents may further enhance antitumor immune response. This phase 1b/3 study will evaluate the safety and efficacy of T-VEC and pembro in patients (pts) with R/M SCCHN progressing after platinum (NCT02626000).

Methods: The primary objective for phase 1b is to assess dose-limiting toxicities (DLTs). Key secondary objectives include objective response rate, best overall response, and safety. Key eligibility criteria include histologically confirmed R/M SCCHN unsuitable for resection/radiotherapy, progressing after platinum tx, and injectable lesions. T-VEC was given by intralesional injection $\leq$ 8 mL of 10^6 PFU/mL on day 1, then after 3 w, $\leq$ 8 mL of 10^8 PFU/mL Q3W; pembro was given IV at 200 mg Q3W. Approximately 18 pts in the safety cohort and an additional 22 pts for long-term safety and efficacy will be enrolled into phase 1b.

Results: 28 pts have been enrolled; 16 are DLT evaluable: 12 (75%) male, median age 57.5 y (range: 35, 77), ECOG 1 (75%). There was a DLT in 1 pt after 2 doses of both drugs: fatal arterial hemorrhage (AH). Grade 3/4 AEs were seen in 6 (38%) of pts - none led to tx discontinuation. There were 2 grade 5 AEs: AH (DLT) and disease progression. Incidence of SAEs possibly related to T-VEC was 5 (31.3%: chills, pyrexia, stridor, odynophagia, AH) and to pembro was 2 (12.5%: eczema, pyrexia) - none led to tx discontinuation.

Table: 1252P

	All DLT Evaluable* (N = 16)	Non-DLT Evaluable (N = 12)	All Pts (N = 28)
All tx-emergent AEs	15 (93.8)	11 (91.7)	26 (92.9)
Grade 3	5 (31.2)	2 (16.7)	7 (25)
Grade 4	1 (6.3)	1 (8.3)	2 (7.1)
Grade 5	2 (12.5)	7 (58.3)	9 (32.1)
AEs related to T-VEC	11 (68.8)	2 (16.7)	13 (46.4)
Grade 3	4 (25)	1 (8.3)	5 (17.9)
Grade 4	0 (0)	0 (0)	0 (0)
AEs related to pembro	9 (56.3)	1 (8.3)	10 (35.7)
Grade 3	1 (6.3)	1 (8.3)	2 (7.1)
Grade 4	0 (0)	0 (0)	0 (0)

*To be DLT evaluable, pt must have had $\geq$ 6 w of follow up from the initial dosing and have received $\geq$ 2 doses of T-VEC and pembro in combination, or have a DLT during the DLT evaluation period after at least 1 dose of T-VEC and pembro.

Conclusions: There was 1 DLT of 16 evaluable pts. The combination regimen was deemed safe to continue into the phase 1b efficacy portion. The protocol was amended to exclude pts who have received reirradiation to the neck and are at high risk for AH.

Clinical trial identification: NCT02626000

Legal entity responsible for the study: Amgen Inc.

Funding: Amgen Inc. and Merck

Disclosure: K. Harrington: Corporate-sponsored research from AstraZeneca, Merck Sharp Dohme; Consulting fees from Amgen, AstraZeneca, Bristol-Myers Squib, Merck, Merck Sharp Dohme, Pfizer; Speakers Bureau from Amgen, AstraZeneca, Bristol-Myers Squib, Merck, Merck Sharp Dohme. S. Treichel, J.J. Kim: Employee and stock shareholder of Amgen Inc. J. Cheng: Employee and stock shareholder of Merck. J. Chesney: Consulting fees from Amgen Inc. All other authors have declared no conflicts of interest.

1253P Characteristics of metastatic melanoma (MM) patients with leptomeningeal disease (LMD) and survival of > 1 year

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Background: Several studies have demonstrated that the presence of LMD correlates with very short overall survival (OS) in metastatic melanoma patients (pts). However, a subset of pts have OS > 12 months (mts). We reviewed the outcomes of a large cohort of patients with LMD to identity predictors of improved outcomes.

Methods: The clinical features, treatments, and OS of MM pts diagnosed with LMD by CSF cytology and/or radiographic findings from 2000 to 2015 were reviewed. Landmark Cox proportional hazard regression models were used to identify factors significantly associated with OS > 12 mts.

Results: 178 pts with LMD were identified. For these, median age at diagnosis (dx) was 51.2 years, 62% were male, 75% pts had a performance status of ECOG 0-1, 39% had elevated LDH, extracranial disease present in 75% and concurrent brain metastasis in 77%. 56% of pts were tested for BRAF mutation, and 37% (of those tested?) were positive. 61% of pts had CSF analysis done, but 49% of these had positive cytology. Neurological deficits were reported in 49%. Median OS from LMD diagnosis was 4.27 mts (95%CI: 3.12-5.55), and 12-, 36-, and 60-mts cumulative OS was 0.22 (95%CI: 0.163-0.290), 0.11 (95%CI: 0.069-0.169), and 0.09 (95% CI: 0.054-0.151), respectively. Compared to those who died within 3 mts, pts who lived longer than 12 mts (n = 36) were more likely to have: ECOG of 0 (57.1% versus 15.3%), previous surgery (55.6% versus 25.3%), systemic disease controlled (41.7% versus 33.3), intrathecal therapy (69.4% versus 21.6%), systemic therapy with targeted therapy (55.6% versus 18.9%) or chemotherapy (61.1% versus 37.8%); and were less likely to have neurological deficits (27.8% versus 62.7%), previous systemic therapy (63.9% versus 88.0%), and LDH above normal (19.4% versus 45.9%). Positive CSF cytology (HR = 3.06, 95% CI 1.02-9.17) and concomitant systemic disease (HR = 2.65, 95%CI 1.03-6.82) were associated with significantly shorter OS.

Conclusions: Long term survival in MM pts with LMD is rare, but possible. Features significantly associated with OS may help strengthen the design and interpretation of future trials for pts with LMD.

Legal entity responsible for the study: Isabella C Glitza

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1254P Tolerance and outcomes of stereotactic radiosurgery combined with anti-PD1 (pembrolizumab) for melanoma brain metastases

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Background: Anti-PD1 antibodies are currently the first-line treatment for patients with metastatic BRAF wild-type melanoma, alone or combined with the anti-CTLA4 mAb, ipilimumab. To date, data on safety and the outcomes of patients treated with the anti-PD1 mAbs, pembrolizumab (PB) or nivolumab, combined with stereotactic radiosurgery (SRS) for melanoma brain metastases (MBM) are lacking.

Methods: Patients with MBM treated with PB combined with SRS between 2012 and 2015 were retrospectively reviewed. The primary endpoint was neurotoxicity. The secondary endpoints were local control, distant intracranial control and overall survival (OS).

Results: Among 74 patients with MBM treated with SRS, 25 patients with a total of 58 MBM treated with PB combined with SRS within 6 months were included. Radionecrosis, occurring within a median time of 6.5 months, was observed in four metastases (6.8%) in four different patients. No significant other SRS-related adverse event had been reported. After a median follow-up of 8.4 months, local control had been achieved in 46 metastases (80%). The median time to local progression was 2 months. Perilesional oedema and intratumour haemorrhage appearing or increasing after SRS were mostly associated with local progression ($P < 0.001$). Median OS was 15.3 months (95% CI 4.6-26). The timing between SRS and PB administration did not seem to influence radionecrosis, intracranial control or OS.

Conclusions: SRS combined with PB was well tolerated and achieved high local control as recently described with SRS and nivolumab. Prolonged OS were achieved compared to that currently yielded with recommended treatments. Prospective studies are required to confirm these results and define the best timing between SRS and PB for the management of MBM.

Legal entity responsible for the study: Caroline Robert, Gustave Roussy

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1255P Dabrafenib and Trametinib combination in real life patients including brain metastases: French experience within MelBase

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Background: Combining BRAF and MEK inhibitors is a standard of care in BRAF-mutated advanced melanoma patients. Dabrafenib (D) and Trametinib (T) have led to a 3-year overall survival (OS) rate around 44% in patients without active brain metastases (BMs) at enrollment. Recently, T received French Health Authority approval but little information is available in D+T combination use in real life, especially with active BMs patients. We report the first results of efficacy and tolerance in real life patients treated with D+T, including BMs, within national French MelBase cohort.

Methods: MelBase is a French multicentric clinical biobank dedicated to the prospective follow-up (FU) of adults with unresectable stage III or stage IV melanoma. Since March 2013, 1168 patients were included (26 centers). Available data were collected (April 2017) and analyzed (demography, OS, progression-free survival (PFS), response rate, safety).

Results: 2 groups are presented: all patients treated with D+T (g1) and patients with BMs treated with D+T (g2). The characteristics at baseline are: - g1 (n = 135): mean age 57 years, PS 0-1 87%, elevated LDH 33%, BRAF V600E mutated 78%, brain metastases 29%, treated in first line 79%. After median FU 11.2 months, median OS and PFS were respectively 17.8 months (95%CI: 15.5-Not Reached (NR)) and 8.1 months (95%CI: 6.2-11.2). Best overall response (BORR) was 63% and disease control rate (DCR) 79%. - g2 (n = 39): mean age 55 years, PS 0-1 87%, elevated LDH 46%, BRAF V600E mutated 72%, treated in first line 73%. After median FU 10.3 months, median OS and PFS were respectively 15.5 months (95%CI: 13.3-NR) and 5.9 months (95%CI: 4.3-10.7). BORR was 56% and DCR 72%.

Conclusions: We report the first real life D+T data in France. Even though our results still need to mature with a longer FU, BORR is similar to COMBI-d updated data (63% g1 *versus* 69%). In addition, our results point out for the first time D+T efficacy in patients with active BMs. Indeed the combination appears more efficient in patients with BMs compared to D alone in already published clinical data (BREAK-MB).

Legal entity responsible for the study: Assistance Publique des Hôpitaux de Paris (AP-HP), Direction Clinique de la Recherche et de l'Innovation (DRCI)

Funding: French National Cancer Institute (INCa), Novartis, Roche, Bristol-Myers Squib, MSD

Disclosure: C. Allayous: Travel, accomodations, expenses: Amgen, Bristol-Myers Squib, Roche. S. Dalac Rat: - Consulting or advisory role: Roche - Travel, accomodations, expenses: Roche, Bristol-Myers Squib, GSK, MSD, Novartis. L. Mortier: Roche, GSK, Novartis, Bristol-Myers Squib, MSD, Amgen. S. Dalle: - Research funding: Bristol-Myers Squib - Travel, accomodations, expenses: MSD, Bristol-Myers Squib P. Saiag: - Honoraria: Bristol-Myers Squib, MSD, Roche, Novartis, Amgen - consulting or advisory role: Bristol-Myers Squib, MSD, Roche, Novartis, Amgen - Research funding: Bristol-Myers Squib, Novartis, Roche - Travel, accomodations, expenses: Bristol-Myers Squib, MSD, Roche Novartis. M. Beylot-Barry: - Consulting or advisory role: Roche, Bristol-Myers Squib - Travel, accomodations, expenses: Roche. F. Aubin: - Honoraria: Abbvie, LéoPharma, MSD, Novartis, Celgène - Consulting or advisory role: Janssen, Celgène, MSD, Roche, Novartis - Travel, accomodations, expenses: Janssen, MSD, Abbvie, Novartis. T. Lesimple: - Consulting or advisory role: Roche, Bristol-Myers Squib, Novartis MSD - Research funding (Institution): Roche - Travel, accomodations, expenses: Roche, MSD. C. Lebbe: - Consultancy, Honoraria, Speakers bureau: Roche, Bristol-Myers Squib, Novartis, MSD, Amgen - Research funding (institution): Roche, Bristol-Myers Squib - Travel accomodations-Meetings: Roche, Bristol-Myers Squib, Novartis, Amgen - Advisory role: Roche, Bristol-Myers Squib, Novartis, MSD, Amgen, GSK. All other authors have declared no conflicts of interest.

1256TiP A Phase II, Randomised, Open Label Study of Neoadjuvant Pembrolizumab with/without Dabrafenib and Trametinib (D+T) in BRAF V600 Mutant Resectable Stage IIIB/C/D Melanoma (NeoTrio Trial)

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Background: BRAF targeted and CTLA-4/PD-1 immunotherapies have high response rates and improve survival for patients (pts) with metastatic melanoma, however, most still die of this disease. It is hypothesised the activated cytotoxic T cell infiltrate that occurs early during treatment with BRAF/MEK inhibitors is potentiated by adding checkpoint inhibitors, resulting in improved response and survival. While trials combining BRAF/MEK inhibitors and anti-PD-1/L1 antibodies are underway in the metastatic setting, the neoadjuvant setting provides an opportunity to test different treatment schedules in small cohorts of pts. Tissue and blood biomarkers can be drawn at several timepoints and correlated to clinical and pathological endpoints to explore mechanisms of response, biomarkers of efficacy, and to select the best schedules to take forward to larger-scale trials.

Trial design: Eligible pts with BRAF V600 mutant, stage IIIB/C/D, resectable and measurable (RECIST 1.1) metastatic melanoma are evenly assigned to 3 cohorts (n = 60). All pts undergo complete macroscopic resection (RES) at week 12 and receive neoadjuvant therapy for 12 weeks preceding RES, followed by 40 weeks of adjuvant therapy. Cohort 1 receive sequential therapy with D+T for 2 weeks, followed by 4 pembrolizumab (pembro) doses until week 12, and 3 weekly pembro after RES. Cohort 2 receive concurrent D+T and 3 weekly pembro before and after RES. Cohort 3 receive 3 weekly pembro for the entire treatment course. Pembro is given at a flat dose of 200mg. Ultrasound surveillance of known disease areas is undertaken during the neoadjuvant period. Serial CT and FDG PET/CT are used to measure response and exclude progression in the neoadjuvant phase, and to monitor for recurrence during adjuvant and post treatment phases. Blood and tumour samples are collected at baseline, week 1, 4 and 12. The primary endpoint is the complete pathological response rate at RES following 12 weeks of therapy. Secondary endpoints include RECIST response, metabolic response, OS, RFS, safety/tolerability, surgical outcomes, quality of life, as well as biomarker analysis.

Clinical trial identification: NCT02858921

Legal entity responsible for the study: Melanoma Institute Australia

Funding: Merck Sharp & Dohme

Disclosure: All authors have declared no conflicts of interest.

1257TiP KEYNOTE 029: Phase 1/2 randomized study of pembrolizumab (pembro) plus 2 dose regimens of ipilimumab (ipi) for advanced melanoma

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Background: Standard-dose pembro (2 mg/kg Q3W) + reduced-dose ipi (1 mg/kg Q3W × 4 doses) showed preliminary efficacy in patients (pts) with melanoma in part 1B of the phase 1/2 KEYNOTE-029 study (NCT02089685), but 42% of pts had treatment-related AEs (TRAEs). In part 1C, 2 more dosing regimens of this combination will be evaluated to further assess efficacy and aim to reduce the toxicity seen in part 1B.

Trial design: Pts aged ≥18 y with histologically confirmed unresectable stage III/IV melanoma not amenable to local therapy; no prior treatment ([neo]adjuvant treatment, excluding PD-1/PD-L1 or BRAF/MEK inhibitors, was allowed if pts did not discontinue for TRAEs, all TRAEs returned to baseline/stabilized, and relapse did not occur within 6 mo of discontinuation for anti–CTLA-4 therapy); measurable disease per RECIST v1.1; ECOG PS 0/1; tumor sample for determination of PD-L1 status; no active brain metastases (baseline brain MRI required) were eligible. ~100 pts will be randomized 1:1 to pembro 200 mg Q3W + ipi 50 mg Q6W (arm 1) or 100 mg Q12W (arm 2). Combination therapy will continue for ≤24 wk in arm 1 and ≤48 wk in arm 2, followed by pembro monotherapy for ≤24 mo or until PD, intolerable toxicity, or patient/physician decision. Tumor imaging will occur every 6 wk until wk 24, and every 12 wk thereafter. Response will be assessed per RECIST v1.1 by independent central review (for efficacy) and modified RECIST v1.1 by investigator review (for treatment decisions). Survival follow-up will occur every 12 wk. AEs will be graded per CTCAE v4.0. Pts with investigator-determined, confirmed CR who received ≥24 wk pembro and ≥2 doses after initial CR may discontinue pembro; pts with investigator-determined, confirmed CR or very good PR (percentage change from baseline in tumor size >60%) who received ≥1 ipi dose may discontinue ipi. Pts with SD or better who subsequently have PD may be eligible for a second course of pembro + ipi or pembro monotherapy (maximum 17 doses pembro and 4 doses ipi). Eligible pts with PD may remain on treatment until a confirmatory scan ≥4 wk later. Primary end points are safety and ORR; secondary end points include PFS, OS, and DOR. Enrollment is ongoing in the US, Australia, and New Zealand.

Clinical trial identification: NCT02089685

Legal entity responsible for the study: Merck & Co., Inc., Kenilworth, New Jersey, USA

Funding: Merck & Co., Inc., Kenilworth, New Jersey, USA

Disclosure: M.B. Atkins: Advisory board member for Bristol-Myers Squibb, Merck, Roche, Novartis, Pfizer, Celldex, Allexion. M.S. Carlino: Advisory board member for Bristol-Myers Squibb, Merck, Amgen, Novartis. Honoraria from Merck, Bristol-Myers Squibb. C.M. McNeil: Advisory board member for Merck, Sharp & Dohme. Speakers bureau for Merck, Sharp & Dohme and Bristol-Myers Squibb. Research funding from Merck, Sharp & Dohme. Travel expenses, including accommodations from Merck, Sharp & Dohme. A. Ribas: Stock ownership in Kite Pharma. Honoraria from Amgen, Pfizer, Merck, Roche. V. Atkinson: Advisory board member: MSD, Bristol-Myers Squib, Novartis, Pierre Fabre. Speakers bureau: MSD, Bristol-Myers Squib, Novartis. Honararia: MSD, Bristol-Myers Squib, Novartis. Travel expenses, including accommodations: MSD, Bristol-Myers Squib, Novartis. M.B. Jameson: Travel expenses, including accommodations for Merck Sharp & Dohme W-J. Hwu: Advisory board member for Merck. Speakers bureau for Merck, Bristol-Myers Squibb, GlaxoSmithKline, MedImmune. J.A. Thompson: Advisory board: CellDex. Research funding to institution: Merck, Agensys, Seattle Genetics, Pfizer. Honoraria: CellDex. J. Anderson: Employment with Merck. B. Homet Moreno: Employee of Merck & Co, Inc. Stock ownership in Merck & Co., Inc. N. Ibrahim: Employment: Merck. Stock: Merck, GSK. G.V. Long: Advisory board member Amgen; Bristol-Myers Squibb; Array; Merck; Merck, Sharp & Dohme; Novartis, Roche, Pierre Fabre. Honararia from Bristol-Myers Squibb; Roche; Merch, Sharp & Dohme. All other authors have declared no conflicts of interest.

1258TiP Phase 2 Study Comparing Pembrolizumab with Intermittent/short-term dual MAPK pathway inhibition plus Pembrolizumab(PEM) in patients harboring the BRAFV600 mutation (IMPemBra Trial)

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Background: Continuous combinations of targeted therapy (TT), e.g. BRAF+MEK inhibitors(BRAFi+MEKi), with immunotherapy (IT), e.g. CTLA-4 or PD-1 blockade are currently tested in several phase1/2 trials with the aim to improve response rate and response duration in melanoma patients with a BRAFV600 mutation. However, high toxicity rates have been observed, revealing PD-1 blockade currently being the only possible combination partner for TT. Recently we have published preclinical data, showing that short-time TT induces strong T cell infiltration and is synergistic with PD-1 blockade. Analysis of biopsies of patients during TT indicate that long-term TT might be counterproductive, as T cell infiltration decreases in some patients already beyond 2 weeks. This raises the question which time period of MAPK pathway inhibition is optimal for combination with anti-PD-1. The IMPemBra trial will address this question, comparing PEM monotherapy with combination schemes of intermittent/short-term BRAFi + MEKi plus PEM. The primary objective is to explore safety, feasibility and the immune-activating capacity of the different regimens.

Trial design: Stage IV BRAFV600E/K mutation positive melanoma patients, naïve for IT and TT, will start treatment with PEM 200mg q3wk. After 6 wks the patients will be randomized (stratified according their LDH level) to continue PEM for up to 2 years (cohort 1), or to one of the experimental cohorts receiving either dabrafenib 150mg BID + trametinib 2mg QD two times intermittent for 1 wk (cohort 2), two times intermittent for 2 wks (cohort 3), or continuous for 6 wks (cohort 4). All cohorts continue afterwards with PEM for up to 2 years. Each cohort will consist of 8 patients. Primary endpoints are SUSARs and adherence to the study timeline, the intra-patient alteration in intratumoral CD8+ T cells and the percentage PD1+ CD8+ T cells in the peripheral blood. Tumor biopsies and blood samples including PBMCs are taken at baseline, wk 6, 9, 12, 18 and in case of progression. Secondary endpoints are objective response rate and progression free survival. Enrollment started in May 2016, 11 patients have been included so far.

Clinical trial identification: NCT02625337

Legal entity responsible for the study: NKI-AVL

Funding: MSD

Disclosure: J.V. Thienen: Advisory board: MSD and Bristol-Myers Squib. J.B. Haanen: Advisory role: Bristol-Myers Squib. MSD, Pfizer, Roche, Novartis, Neon Therapeutics Research grants: Bristol-Myers Squib, MSD, GSK. C.U. Blank: Advisory board: Bristol-Myers Squib, MSD, Novartis, GSK, Pfizer, Lilly, Roche Research grants: Bristol-Myers Squib, Novartis. All other authors have declared no conflicts of interest.

1259TiP A randomized, double-blind, placebo-controlled, phase III study comparing the combination of PDR001, dabrafenib and trametinib versus placebo, dabrafenib and trametinib in previously untreated patients with unresectable or metastatic BRAF V600–mutant melanoma (COMBI-i)

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Background: Checkpoint inhibitor and targeted therapies are both important tools in the management of *BRAF* V600–mutated unresectable or metastatic melanoma. Although these therapies have improved responses and overall survival, many patients still progress and die from this disease. Thus, additional treatment strategies are needed to improve durability of responses and related long-term outcomes in these patients. Based on preclinical and preliminary clinical data, BRAF and MEK inhibitors can reverse the oncogenic BRAF-induced immune-suppressive phenotype through enhanced melanoma antigen expression and enhanced tumor antigen-specific T-lymphocyte recognition in vivo. These data suggest that there is potential clinical benefit in combining dabrafenib and trametinib with checkpoint inhibitor therapy.

Trial design: The 3-part COMBI-i phase 3 study (NCT02967692) will evaluate the safety and efficacy of PDR001, an investigational anti–programmed death 1 antibody, in combination with dabrafenib and trametinib in previously untreated patients with *BRAF* V600–mutated unresectable or metastatic melanoma. In part 1, a safety run-in will establish the recommended phase 3 regimen (RP3R) for use in part 3 using an adaptive Bayesian logistic regression model. In part 2, tissue and blood samples from the biomarker cohort will be used to characterize baseline immune markers and explore potential immune marker modulation by the triplet therapy. Part 3 is the randomized, double-blind, placebo-controlled portion that will open once the RP3R has been determined. Approximately 500 patients will be randomized 1:1 to receive either PDR001 in combination with dabrafenib and trametinib or placebo in combination with dabrafenib and trametinib, with randomization stratified based on Eastern Cooperative Oncology Group performance status and lactate dehydrogenase level. The primary endpoint will be progression-free survival per investigator's assessment according to RECIST v1.1. Overall survival will be a key secondary endpoint.

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Legal entity responsible for the study: Novartis Pharmaceuticals Corporation

Funding: Novartis Pharmaceuticals Corporation

Disclosure: E. Gasal: Employment: Novartis Stock or Other Ownership: Amgen Inc, Novartis. A.M. Arance Fernandez: Honoraria, Consulting/Advisory Role, and Speakers Bureau: Roche, Bristol-Myers Squibb, MSD, and Novartis Travel/Accommodations/Expenses: Roche, Bristol-Myers Squibb P.A. Ascierto: Consulting/Advisory Role: Bristol-Myers Squibb, Roche/Genentech, Merck Sharp & Dohme, Novartis, Amgen, Array BioParma, Merck Serono Research Funding: Bristol-Myers Squibb, Roche/Genentech, Array BioPharma. V. Atkinson: Honoraria and Speakers Bureau: Bristol-Myers Squibb, MSD, Novartis, Roche Consulting/Advisory Role: Bristol-Myers Squibb, MSD, Novartis, Pierre Fabre Travel/Accommodations/Expenses: Bristol-Myers Squibb, MSD, Novartis. R. Dummer: Honoraria and Consulting/Advisory Role: Roche, Bristol-Myers Squibb, MSD, Novartis, GlaxoSmithKline, Amgen, Takeda, Pierre Fabre Research Funding: Roche, GlaxoSmithKline, Bristol-Myers Squibb, Novartis, MSD, Takeda, Pierre Fabre. K.T. Flaherty: Consulting/Advisory Role: Novartis. J-J. Grob: Honoraria and Consulting/Advisory Role: Bristol-Myers Squibb, Roche, MSD, Novartis Speakers Bureau: Novartis Travel/Accommodations/Expenses: Bristol-Myers Squibb, MSD, Roche, Novartis. J. Hansson: Consulting/Advisory Role: Roche, Novartis, Merck, Bristol-Myers Squibb Travel/Accommodations/Expenses: Novartis. J. Hassel: Honoraria: Bristol-Myers Squibb, MSD, Roche, GlaxoSmithKline, Novartis, Amgen Research Funding: Bristol-Myers Squibb Travel/Accommodations/Expenses: Bristol-Myers Squibb, MSD, Amgen, GlaxoSmithKline. J. Larkin: Honoraria: Bristol-Myers Squibb, MSD, Pfizer, Novartis, Eisai, GlaxoSmithKline, Roche Research Funding: Bristol-Myers Squibb, MSD, Pfizer, Novartis. C. Lebbé: Honoraria, Consulting/Advisory Role: Roche, Bristol-Myers Squib, Novartis, Amgen, MSD Speakers Bureau: Bristol-Myers Squib, Amgen, Roche, Novartis Research Funding: Roche, Bristol-Myers Squib Travel/Accommodations/Expenses: Roche, Bristol-Myers Squib, Amgen. G.V. Long: Consulting/Advisory Role: Bristol-Myers Squibb, Merck, Novartis, Amgen, Roche P. Lorigan: Consulting/Advisory Role: Merck Sharp & Dohme, Bristol-Myers Squibb, Novartis, Amgen, GlaxoSmithKline Speakers Bureau: Merck Sharp & Dohme, Novartis, Bristol-Myers Squibb, Roche Travel/Accommodations/Expenses: Merck Sharp & Dohme, Bristol-Myers Squibb. W. Miller: Honoraria: Bristol-Myers Squib, Merck, Roche, Novartis, GlaxoSmithKline Consulting/Advisory Role: Bristol-Myers Squib, Merck, Roche, Novartis, Amgen, GlaxoSmithKline Research Funding: Bristol-Myers Squib, Novartis, GlaxoSmithKline, Roche, AstraZeneca, Merck, MethylGene, Bayer, Amgen, MedImmune. P. Nathan: Consulting/Advisory Role: AztraZeneca, Bristol-Myers Squibb, MSD, Immunocore, Pfizer, Pierre Fabre, Novartis, GlaxoSmithKline, Ispen Speakers Bureau: Bristol-Myers Squibb, Novartis Travel/Accommodations/Expenses: Bristol-Myers Squibb, MSD. A. Ribas: Consulting/Advisory Role: Merck, Amgen, Genentech/Roche, Novartis, Lilly Stock or Other Ownership: Kite Pharma, Compugen, FLX Bio, CytomX Therapeutics, Arcus Ventures. C. Robert: Honoraria and Consulting/Advisory Role: Bristol-Myers Squibb, Roche, Merck, Novartis, Amgen, GlaxoSmithKline. D. Schadendorf: Honoraria, Speakers Bureau and Travel/Accommodations/Expenses: Amgen, Bristol-Myers Squibb, Novartis, MSD, Roche Consulting/Advisory Role: Bristol-Myers Squibb, Novartis, MSD, Roche, Array Research Funding: Bristol-Myers Squibb, Novartis. H. Tawbi: Consulting/Advisory Role: Novartis Research Funding: Bristol-Myers Squibb, Novartis, Merck. A. Upalawanna: Employment and Stock or Other Ownership: Novartis.

1260TiP Late physical, psychological and social consequences of ipilimumab treatment in advanced melanoma

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Background: After the introduction of ipilimumab, an anti-CTLA-4 monoclonal antibody, durable, long term survival has become a possibility for a subgroup of advanced melanoma patients. Since ipilimumab is a relatively novel drug there are limited data on the long-term physical, psychological, and social functioning of these patients. This study will evaluate the long-term physical and psychosocial performances and the information needs of advanced melanoma survivors who have been treated with ipilimumab.

Trial design: This is a prospectively enrolling, multicentre cohort study. **Objectives:** To assess health-related quality of life (HRQoL), anxiety, depression, fatigue, fear of cancer recurrence, sexual health and generic health status in patients with advanced melanoma who have survived at least 2 years after ipilimumab treatment (without subsequent other systemic therapies) as compared with healthy controls, and to describe the melanoma-specific HRQoL, impact of cancer, social functioning and information needs in patients with advanced melanoma who have survived at least 2 years after ipilimumab treatment. **Patients and healthy control population:** Patients with advanced (stage IV or unresectable stage III) melanoma who survived at least 2 years and were treated with ipilimumab between 2011 and 2015 in 14 hospitals in the Netherlands are included. The patient population consists of 3 treatment groups based on time since ipilimumab treatment: 24 to $<$ 36 months, $\geq$ 36 to $<$ 48 months and $\geq$ 48 months post-ipilimumab treatment. The healthy control population will be selected from 'Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship (PROFILES)'. PROFILES contains a reference cohort of more than 2000 healthy individuals and is designed to be representative of the Dutch-speaking population in the Netherlands. **Measurements:** The primary and secondary study outcomes will be measured by questionnaires, at 3 time-points in patients 24 to $<$ 36 months and at 1 time-point in patients $\geq$ 36 months post-ipilimumab treatment. The primary outcome, HRQoL will be assessed with the European Organisation for Research and Treatment of Cancer quality of life questionnaire-C30 (EORTC QLQ-C30).

Clinical trial identification: Date of release: November 2016

Legal entity responsible for the study: Netherlands Cancer Institute

Funding: Bristol-Myers Squibb

Disclosure: A.H. Boekhout: Employee of Bristol-Myers Squibb. M. Lee, KJM Janssen: Employee of and receiving stock from Bristol-Myers Squibb, during the conduct of the study. All other authors have declared no conflicts of interest.

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NEW DIAGNOSTIC TOOLS

1261P mRNA capture sequencing enabled liquid biopsy screening

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Background: In contrast to general belief, a substantial part of the human protein coding transcriptome is abundantly present in the blood as extracellular mRNA, ready to exploited. It is well known that cancer cells actively and passively release RNA cargo into circulation and their detection may inform on the patient disease status.

Methods: We developed and applied a probe based RNA capture sequencing method as a sensitive RNA sequencing workflow to study thousands of transcripts in cell-free RNA from cancer patients' plasma. The method is based on exome-style enrichment of a randomly primed cDNA library with preservation of strandedness information. More than one million capture probes target 21,000 human messenger RNA and 60,000 human long non-coding RNA genes. Apart from RNA abundance profiling, this type of data can also be used to detect structural RNA variants, such as somatic mutations, fusion genes, and RNA editing events, all known to play an important role in cancer.

Results: On average, between 6000-10,000 RNA genes are reproducibly detected in 0.2 ml of plasma. Detection and coverage sensitivity is greatly increased by using larger plasma volume and improved adaptor ligation strategies. We also observed a positive correlation between number of platelets in plasma and detected genes and variants, in line with their tumor-educated nature. Our benchmarked RNA variant pipeline identifies thousands of germline and somatic variants in circulating mRNA. A dedicated titration experiment in which plasma from cancer and healthy individuals were mixed in known ratios demonstrates excellent quantitative performance. Pronounced RNA abundance differences and enriched pathways are observed between cancer types and during treatment. The RNA capture sequencing also works on other body fluids, such as urine and serum, and simultaneous targeting of mRNA and lncRNA provides substantial enrichment of otherwise low-abundant lncRNAs.

Conclusions: RNA capture sequencing of liquid biopsies is a promising new application to support precision oncology and is expected to enhance therapy stratification, treatment response monitoring and early detection of relapse.

Legal entity responsible for the study: Biogazelle and Ghent University

Funding: Biogazelle, Illumina

Disclosure: J. Vandesompele: Apart from professorship at Ghent University, co-founder and part-time CSO at Biogazelle, a Ghent University spin-off company.

1262P Use of droplet digital PCR for quantitative and automatic analysis of the HER2 status in breast cancer patients

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Background: Digital polymerase chain reaction (dPCR) has been used to yield an absolute measure of nucleic acid concentrations. Recently, a new method referred to as droplet digital PCR (ddPCR) has gained attention as a more precise and less subjective assay to quantify DNA amplification. We demonstrated the usefulness of ddPCR to determine HER2 gene amplification of breast cancer.

Methods: In this study, we used ddPCR to measure the HER2 gene copy number in clinical formalin-fixed paraffin-embedded samples of 41 primary breast cancer patients. To improve the accuracy of ddPCR analysis, we also estimated the tumour content ratio (TCR), the ratio of tumour cell count per section, for each sample.

Results: Our determination method for HER2 gene amplification using the ddPCR ratio (ERBB2:ch17cent copy number ratio) combined with the TCR showed high consistency with the conventionally defined HER2 gene status according to ASCO-CAP (American Society of Clinical Oncology/College of American Pathologists) guidelines ($P < 0.0001$, Fisher's exact test). The equivocal area was established by adopting 99% confidence intervals obtained by cell line assays, which made it possible to identify all conventionally HER2-positive cases with our method. In addition, we succeeded in automating a major part of the process from DNA extraction to determination of HER2 gene status.

Conclusions: The introduction of ddPCR to determine the HER2 gene status in breast cancer is feasible for use in clinical practice and might complement or even replace conventional methods of examination in the future.

Legal entity responsible for the study: The University of Tokyo

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1263P BRCA1 large gene rearrangements (LGRs) in Russian breast cancer patients: the development of the droplet digital PCR assay for LGR detection and the identification of recurrent exon 8 deletions

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Background: Some pathogenic BRCA1 mutations are represented by large gene rearrangements (LGRs). LGRs cannot be detected by conventional Sanger sequencing. Multiplex ligation-dependent probe amplification (MLPA) is a leading method for LGR detection, however it is entirely based on the use of commercial kits, includes relatively lengthy hybridization step and is poorly suitable for the large-scale screening for recurrent deletions.

Methods: We developed and validated the droplet digital PCR (ddPCR) assay, which covers the entire coding region of BRCA1 gene and is capable to precisely quantitate the copy number for each exon.

Results: 141 breast cancer (BC) patients, who demonstrated evident clinical features of hereditary BC but turned out to be BRCA1/2 mutation-negative upon Sanger sequencing, were subjected to the LGR analysis. 4 patients with LGR were identified, with 3 cases of exon 8 deletion and 1 women carrying the deletion of exons 3-7. Excellent concordance with MLPA was observed. Exon 8 copy number was tested in additional 720 high-risk BC, and another 3 cases with the deletion were revealed; MLPA re-analysis demonstrated that exon 8 loss was a part of a larger genetic alteration in 2 cases, while the remaining patient had isolated defect of exon 8. Long-range PCR and next generation sequencing revealed, that 3 out of 4 samples with isolated exon 8 deletion had an identical rearrangement.

Conclusions: Droplet digital PCR is a reliable tool for detection of large gene rearrangements. BRCA1 LGRs are rare in Russian hereditary BC patients, with exon 8 deletion being a recurrent allele in this population.

Legal entity responsible for the study: Laboratory of Molecular Oncology, N.N. Petrov Institute of Oncology, St.-Petersburg

Funding: Russian Science Foundation (grant 14-25-00111)

Disclosure: All authors have declared no conflicts of interest.

1264P Clinical evaluation of low density array based EGFR mutation detecting kit using tissue samples and liquid biopsies

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Background: The information on EGFR mutations status improves the benefit of targeted therapies for the non-small-cell lung cancer patients. These determinations are already part of standard protocols for cancer treatment. The study of the mutations in EGFR in liquid biopsy also permits a follow-up throughout the treatment and detection of acquired resistance.

Methods: CLART® CMA EGFR kit (GENOMICA, Spain) detects the 40 high-prevalence mutations associated with sensitivity or resistance to the treatment. These mutations are located in the exons 18, 19, 20 and 21. The kit is based on the multiplex ARMS-PCR followed by detection on a low-density microarray platform: CLART® (Clinical Arrays Technology). The samples were processed in a bench-top semi-automated system, Autoclart. A new version of the kit, CLART® CMA EGFR LB, allows using liquid biopsy as a sample with only an additional pre-PCR step.

Results: A 107 tissue biopsies from metastatic NSCLC patients were obtained and analyzed in two University Hospitals in Spain: Vall d'Hebron (Barcelona) and 12 de Octubre (Madrid). The EGFR mutations were detected with CLART® CMA EGFR kit with 96.3% concordance with the routine methods used in the hospital practice (Cobas/Therascreen/Sanger sequencing). The discrepant results were analyzed by Sanger sequencing. The sensitivity of the CLART® CMA EGFR kit is 100% and specificity is 96.5%. The same CLART platform, only with the addition of one pre-PCR amplification step was used for processing the plasma samples (liquid biopsy) from the NSCLC metastatic patients. A total of 8 samples were tested. In six samples the results obtained from tissue samples and liquid biopsies were concordant. In the two discordant samples the exon 19 deletions detected in tissue were not detected in plasma samples. The wt results obtained for these two liquid biopsies were confirmed by Next Generation Sequencing.

Conclusions: Given the high specificity and sensitivity and excellent concordance with the other platforms in hospital practice, CLART® CMA EGFR kit is valid for the use in

the clinical routine. Furthermore, using the same semi-automated platform for tissue samples and liquid biopsy facilitates laboratory work and reduces turnover time per sample.

Legal entity responsible for the study: GENOMICA

Funding: GENOMICA

Disclosure: All authors have declared no conflicts of interest.

1265P Correlation of somatic genomic alterations between tissue genomics and circulating tumor DNA (ctDNA) employing next generation sequencing (NGS) analysis in lung and gastrointestinal cancers

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Background: Peripheral blood circulating tumor DNA (ctDNA) and tumor tissue next-generation sequencing (NGS) is routinely performed to guide therapy in cancer patients. However, little is known about the concordance or discordance between commercially available tissue genomics testing panels and ctDNA. The aim of our study was to assess concordance between matched cancer tissue genomics and blood based ctDNA in lung and gastrointestinal (GI) cancers.

Methods: Tissue genomic analysis was performed with Paradigm® (n = 17)/Caris® (n = 11) and ctDNA was analyzed with Guardant360® (n = 28). Samples included, non-small cell lung cancer (n = 10), small cell lung cancer (n = 4), colorectal cancer (n = 5), hepatocellular carcinoma (n = 2), intrahepatic cholangiocarcinoma (n = 1), pancreatobiliary adenocarcinoma (n = 3), esophageal adenocarcinoma (n = 2) and gastric adenocarcinoma (n = 1).

Results: We identified 6 (21%) patients with at least one gene mutation that was detected by both tissue genomic and ctDNA analysis. Total number of gene mutations identified in 28 patients were 106, but only 8 (7.5%) were detected by both tissue and ctDNA panels. When this testing was done within 90 days the concordance increased to 10.20%. Table.

Table: 1265P

Patients with at least one mutation detected by both platforms	21% (n = 6/28)
Mutations detectable by both platforms	7.54% (n = 8/106)
Mutations detectable by both platforms if interval between tissue and blood collection <90 days.	10.20% (n = 5/49)

Conclusions: We identified significant discordance between tissue and ctDNA mutational profiles in lung and GI cancers. Therefore, the results from NGS platforms should be interpreted with extreme caution. Our analysis reveals that these platforms should not be used interchangeably. The discordance rate may be due to tissue heterogeneity and/or spatial and temporal clonal evolution. Standardization of the sequencing techniques and education of practicing oncologists about the limitations of liquid biopsies needs to be highlighted.

Legal entity responsible for the study: Saint Luke's Health System

Funding: None

Disclosure: J. Subramanian: Paradigm Advisory board. All other authors have declared no conflicts of interest.

1266P Analytical and clinical validation of a next-generation sequencing-based circulating tumor DNA (ctDNA) assay assures its clinical application

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Background: To date, ctDNA has been exhibiting its unprecedented translational potential in cancer care. However, accurate identification of comprehensive genomic alternations is rigorously needed for its clinical utility.

Methods: Three biologically relevant reference materials with allele frequencies expected at 0.1%, 1% and 5% were used to analytically evaluate the accuracy and reproducibility. Clinically, 43 ctDNA samples from lung, liver, colorectal, breast and gastric cancers were genomically profiled and compared to the known alternations in their matched solid tumors, in terms of single base substitution, insertions/deletions, copy number variations and rearrangement.

Results: The analytical validation demonstrated unprecedented accuracy: near 100% specificity (99.6%, 99.9% and 100%) and 95.8%, 100% and 100% sensitivity for 3 reference materials, respectively. The actual detection limit was as low as 0.05%. The reproducibility was assessed as 0.998 (jaccard index) by sequencing 2 replicates of each reference. In clinical validation, compared to matched FFPE results, this ctDNA assay showed overall 99.9% specificity and 89% sensitivity, with > 90% sensitivity when only drug-gable hotspots were concerned. Eight events of gene rearrangements involving known targeted genes of ALK (n = 4), ROS1 (n = 3) and MET (n = 1) were detected from seven patients with 100% sensitivity and 100% specificity, confirmed either by IHC or panel sequencing (depth > 1,000X) over their matched FFPE biopsies. Due to its typically low abundance, CNV from ctDNA was detectable only for those highly amplified genes (> =8 copies) with > =4 exons, demonstrating 72.2% sensitivity and 99.5% specificity.

Conclusions: Stringent criteria for both analytical and clinical validations are required for clinical utility of ctDNA. Our ctDNA assay has demonstrated high accuracy and reliability in comprehensively genomic profiling of ctDNA, especially in regard to drug-gable targets, which assures its translational utility in optimizing and monitoring targeted therapies in cancer management.

Legal entity responsible for the study: OrigiMed Inc

Funding: OrigiMed Inc

Disclosure: W. Liu, S. Mu, J. Yao, H. Chen, Z. Hu, J. Hu, G. Chirn, H. Kang, K. Wang, M. Yao: Employee of OrigiMed Inc.

1267P Combination of solid and liquid biopsy genomic profiling for tumor heterogeneity characterization

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Background: Characterization of inter- and intra-tumoral heterogeneity has become a central issue in the implantation of personalized medicine. In this sense, although, the liquid biopsy has been recognized as a promising tool for prognostic, molecular profiling and monitoring of cancer disease, we are still at the beginning of its incorporation alone into the routine oncology practice. In the present study, we evaluate the usefulness of an integrated approach that combines the analysis of both solid (FFPE block) and liquid (blood sample) biopsy, into the clinical routine.

Methods: We analyzed 163 samples of metastatic patients, with different cancers types, using the OncoSTRAT&GO® solution (Biosequence SL, Valencia, Spain through OncoDNA SA, Gosselies, Belgium); that allows i) sequencing of more than 200 genes, identification of 350 genes fusion and evaluation of the expression level of tens of proteins in solid biopsy and ii) sequencing of hotspot mutations of a 27-gene panel in liquid biopsy.

Results: We focus the analysis on those actionable variants that could be detected in both solid and liquid biopsies. A complete concordance of 62.6% was observed between both types of biopsies variants. The minimum variant allele frequencies (VAFs) was found to be 0.1% and 1% in liquid and solid biopsy, respectively. The concordant and discordant VAFs were compare showing similar distributions, no significant statistical differences were found: mean values of 14.5/8.9% (P = 0.79; Mann-Whitney test) and 39.4/29.9% (P= .08; Mann-Whitney test) in liquid and solid biopsy, respectively.

Conclusions: Our findings indicate that the combination of solid and liquid biopsies analysis in clinical practice provides additional information in 37.4% of the cases. Discordant variants cannot be put down to the sensibility of the analysis and consequently should be associated to tumor heterogeneity, low tumor burden and/or treatment response. Our results show the usefulness of an integrated approach, resulting in a broad characterization of the tumor for a better disease management.

Legal entity responsible for the study: Translational Oncology Division, Oncohealth Institute, IIS-Fundacion Jimenez Diaz-UAM, Madrid, Spain

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1268P Retrospective analysis of a SHIVA01 trial cohort using functional mutational analysis successfully predicted treatment outcome

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Background: The SHIVA01 trial was a randomized proof-of-concept phase II trial, testing the hypothesis of treating patients (pts) based on molecular profiles with molecularly targeted agents (MTA) in a histology agnostic manner. The trial results

showed no statistically significant difference in PFS between MTA and control arm. The addition of functional information on identified mutations and their response to MTA's may improve treatment outcomes.

Methods: The molecular profile of 20 pts treated with a MTA in the trial was analyzed in the NovellusDx Functional Annotation for Cancer Treatment (FACT), a functional mutational analysis platform, to reveal activated signaling pathways and measure the activity of these mutations in the presence of the MTA's administered in the trial. The results of FACT were used to stratify the pts into responders and non-responders.

Results: We uncovered the functional landscape in 12 of the 20 pts in the analyzed group. In the remaining 8 pts, no relevant mutational alterations were identified. This analysis provided experimental evidence to the oncogenic activity of the mutations and of the combination of mutations identified in the pts. Furthermore, the response of these pts' mutations to the MTA's used was measured in-vitro, blinded to the actual clinical results. Each patient was then assigned as either a responsive or non-responsive. When the results were used to stratify the pts' PFS data, positive patients had a median PFS of 5.8 months vs. 1.7 months in the negative group ($P = 0.03$ in a non-parametric test).

Conclusions: This analysis shows the predictive power of a new and innovative method for characterization of pts molecular profiles and their in-vitro response to MTA's. The abundance of mutations classified as VUS and multiple mutations in different genes reveals the complexity in assigning the optimal MTA and the necessity of a functional assay. The FACT analysis accurately provided prognostic predictions of the pts treated into responsive and pts with no molecular basis for a benefit in MTA treatment. Importantly, the hypothesis driving the SHIVA01 trial proved positive by the addition of the functional interpretation of the mutational data.

Legal entity responsible for the study: Institute Curie, Paris, France

Funding: None

Disclosure: G. Tarcic, O. Edelheit, Z. Barbash, M. Vidne, B. Miron: A full time employee of NovellusDx. All other authors have declared no conflicts of interest.

1269P Integrative multi-platform meta-analysis of gene expression profiles in pancreatic ductal adenocarcinoma patients for identifying novel diagnostic biomarkers

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Background: Applying differentially expressed genes (DEGs) to identify feasible biomarkers in diseases can be a hard task when working with heterogeneous datasets. Expression data are strongly influenced by technology, sample preparation processes, and/or labeling methods. The proliferation of different microarray platforms for measuring gene expression increases the need to develop models able to compare their results, especially when different technologies can lead to signal values that vary greatly. Integrative meta-analysis can significantly improve the reliability and robustness of DEG detection. The objective of this work was to develop an integrative approach for identifying potential cancer biomarkers by integrating gene expression data from two different platforms. Pancreatic ductal adenocarcinoma (PDAC), where there is an urgent need to find new biomarkers due its late diagnosis, is an ideal candidate for testing this technology.

Methods: Expression data from two different datasets, namely Affymetrix and Illumina (18 and 36 PDAC patients, respectively), as well as from 18 healthy controls, was used for this study. A meta-analysis based on an empirical Bayesian methodology (ComBat) was then proposed to integrate these datasets. DEGs were finally identified from the integrated data by using the statistical programming language R.

Results: After our integrative meta-analysis, 5 genes were commonly identified within the individual analyses of the independent datasets. Also, 28 novel genes that were not reported by the individual analyses ('gained' genes) were also discovered. Several of these gained genes have been already related to other gastroenterological tumors.

Conclusions: The proposed integrative meta-analysis has revealed novel DEGs that may play an important role in PDAC and could be potential biomarkers for diagnosing the disease.

Legal entity responsible for the study: Grupo de Tratamiento de Tumores Digestivos

Funding: Grupo de Tratamiento de Tumores Digestivos

Disclosure: M. Benavides: Received honoraria from Roche and honoraria for advisory role from Roche. C. Guillen-Ponce: Received honoraria from Roche; honoraria for advisory role from Roche Pharma, Bayer, Merck Serono, Sanofi Aventis, Celgene y Novocure; other remuneration from Celgene, Roche Pharma, Sanofi Aventis, Merck Serono. E. Aranda Aguilar: Received honoraria for advisory role from Amgen, Bayer, Celgene, Merck, Roche, Sanofi. All other authors have declared no conflicts of interest.

1270P 3D Cultured Tumour from Patients to Predict Treatment Response

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Background: Treatment selection for cancer patients is still a challenge. Average response rates for standard chemotherapy are low due to a lack of predictive markers. Genetic approaches to improve treatment efficacy have not yet delivered solutions for the day-to-day clinic. Functional testing of 3D cultures of patient tumour biopsies has the potential to identify tumours that are sensitive to standard drugs, search for alterative drugs when treatment options appear exhausted, and prevent overtreatment. Our technology based on image analysis of 3D tumour cultures accommodates accurate evaluation of drug sensitivity with small amounts of heterogeneous tumour material. We aim to validate our methods, and develop diagnostics to predict drug response for cancer patients.

Methods: 3D cultures embedded in a protein-rich hydrogel are generated from tumour biopsies, and exposed to standard-of-care therapies, targeted therapies and drug combinations. An automated high content screening platform measures cell and tissue morphology, and reports responses such as tumour cell killing, growth arrest and local invasion. Per tumour type and drug, morphological features are selected as standard read-outs for the response. Proof of Concept (PoC) trials have been initiated to compare drug sensitivity of tumour cultures with treatment response in the clinic.

Results: We present results of PoC experiments showing drug sensitivity in 3D cultures of fresh and cryopreserved tumour material of gastric, endometrial, cervical, and ovarian cancer patients. Standard-of-care therapies were tested and results were compared per drug (combination). Differentiated drug responses are identified for treatment schedules including platinum-based drugs, taxanes, anthracyclines, 5-FU. In addition, responses to drugs that are not (yet) considered standard of care (PARP inhibitors) were measured.

Conclusions: Our technology enables drug sensitivity testing in 3D cultures of tumour tissues. This allows patient-specific treatment responses to developmental and standard-of-care drugs to be determined. Ongoing PoC trials will reveal the correlation of our in vitro test with treatment responses in the clinic.

Legal entity responsible for the study: VitroScan B.V.

Funding: VitroScan B.V.

Disclosure: All authors have declared no conflicts of interest.

1271P 5-ALA administration for photodynamic diagnosis of peritoneal metastases due to advanced gastric cancer: A randomised, double-blind, multicentre phase I/II study

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Background: For advanced gastric cancer, diagnosis of peritoneal dissemination is mandatory prior to the decision of therapy; therefore, staging laparoscopy (SL) has gained wider clinical acceptance. We have reported the efficacy of SL with photodynamic diagnosis (PDD) using 5-aminolevulinic acid (5-ALA). In this study, the safety and effectiveness of oral administration of 5-ALA PDD compared with that of conventional white-light laparoscopic diagnosis is assessed in a phase I/II study. This research also used a randomised double-blind comparison to explore the optimum dose of 5-ALA to be followed by a confirmatory study.

Methods: Subjects were patients with type 3 or 4 gastric cancer. A total of 20 or 40 mg/kg 5-ALA was administered orally 180–300 minutes before SL. The primary endpoint was safety; the secondary endpoints were sensitivity, specificity, positive predictive value, negative predictive value, and the proportion of patients with peritoneal dissemination.

Results: Thirty-one patients, comprising 19 men and 12 women, were enrolled. Fourteen patients were allocated to the 20 mg/kg group and 17 to the 40 mg/kg group. The median age was 70 years. The proportions of adverse events were 53.8% and 41.2% in the 20 and 40 mg/kg groups, respectively. Hypotension was noted as serious adverse event in 1 patient. The sensitivities of PDD in the 20 and 40 mg/kg groups were higher (95.7% and 100%, respectively) than those of conventional diagnosis (73.9% and 67.8%) ($p = 0.0625$ and $p = 0.0313$). In terms of precision, the evaluation values of diagnosis through conventional imaging compared with PDD were as follows: sensitivity, 83.5% vs. 98.6%; specificity, 75.5% vs. 38.8%; positive predictive value, 82.2% vs. 69.6%; and negative predictive value, 75.5% vs. 95.0%, respectively. In addition, one more patient was found positive for dissemination via PDD.

Conclusions: This investigator-initiated clinical trial confirmed the safety and effectiveness of 5-ALA administration in PDD for peritoneal metastases in gastric cancer. Results indicated that both doses of 5-ALA may be clinically applicable. Thus, we are now conducting a confirmatory study to apply for pharmaceutical approval of 5-ALA.

Clinical trial identification: JMA-IIA00225

Legal entity responsible for the study: Prof. Yuichiro Doki

Funding: This work was supported by the clinical trial promotion pro-gram subsidized by the Japan Medical Association with theMinistry of Health, Labour and Welfare Research Grant

Disclosure: All authors have declared no conflicts of interest.

1272P Diagnostic performance of dedicated breast PET scanner with a ring detector

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Background: Dedicated breast positron emission tomography scanners (dbPET) have been developed to make possible higher spatial resolution and sensitivity. The purpose of this study was to investigate the diagnostic performance of a dbPET scanner with an O-shaped detector in patients with known breast cancer.

Methods: A total of 82 female patients diagnosed with breast cancer consented to participate in this study (84 lesions: 10 ductal carcinomas in situ (DCIS), 74 invasive cancers). All patients underwent a WB-PET/MRI using Biograph mMR® (Siemens Healthcare) approximately 80 minutes after fluorine-18 fluorodeoxyglucose ((18)F-FDG;3.0MBq/kg) injection, followed by dbPET using Dedicated Breast PET System Elmammo®(Shimadzu, Kyoto, Japan) which required 5 minutes per breast.

Results: The overall imaging sensitivities of dbPET and WB-PET/MRI were 89% (75/84) and 87% (74/84) respectively. The sensitivities excluding 5 lesions which were outside the field of view of dbPET, were 95% (75/79) and 87% (69/79) respectively. The standardized uptake values (SUV) of dbPET (SUVmax mean13, range 1.64-41.6) and WB-PET/MRI (SUVmax mean 5.71, range 1.15-13.3) showed correlation with nuclear grade (NG) (Spearman's rank-correlation coefficient $r = 0.507, 0.455, p < 0.001$), Ki67 ($r = 0.56, 0.62, p < 0.001$) and estrogen receptor ($r=-0.524, -0.475, p < 0.001$). The sensitivities for DCIS were 90% (9/10), 60% (6/10) respectively. The sensitivities for DCIS and invasive cancers with 1cm or less maximal diameter were 86% (18/21) and 57% (12/21) respectively. We observed six lesions (three high grade DICS (1.7 cm - 5cm), three high grade invasive cancers with 0.3-0.9cm) that were only detected by dbPET. On the contrary, four lesions could not be detected by either modality (low grade DCIS, invasive lobular carcinoma;2cm, low grade invasive ductal carcinoma with 0.6cm).

Conclusions: Both dbPET and WB-PET/MRI showed high imaging sensitivity, but dbPET had significantly higher sensitivity to high grade DCIS and invasive lesions up to 1cm. This level of diagnostic performance could help to detect early stage cancers as part of breast screening.

Clinical trial identification: We have registerd this trial at UMIN (Univresity Hospital Medical Information network) -CTR Serch Clinical Trials This trial protocol number of UMIN; UMIN000027227 (https://upload.umin.ac.jp/cgi-open-bin/ctr_e/index.cgi) Release date; 02.May.2017

Legal entity responsible for the study: Japan

Funding: Shimadzu corporation

Disclosure: All authors have declared no conflicts of interest.

1273O Results of the phase III IFCT-0302 trial assessing minimal versus CT-scan-based follow-up for completely resected non-small cell lung cancer (NSCLC)

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Background: Several guidelines recommend a follow-up based on clinic visits and chest CT-scans for completely resected NSCLC. However, evidence to support these recommendations is poor, in the absence of randomized data. The IFCT-0302 trial is a randomized multicenter trial which compared 2 follow-up programs for completely resected stage pI, II, IIIA and T4 (pulmonary nodules in the same lobe) N0-2 NSCLC (TNM 6th edition).

Methods: In the control arm (arm 1), follow-up consisted of clinical examination and Chest X-ray (CXR). In the experimental arm (arm 2), patients underwent clinical examination, CXR, thoraco-abdominal CT-scan (CT) plus bronchoscopy (optional for adenocarcinomas). In both arms, procedures were repeated every 6 months after randomization during the first 2 years, and yearly until 5 years. Supplementary procedures were allowed in case of symptoms. The primary endpoint was overall survival (OS).

Results: Between January 2005 and November 2012, 1775 patients were randomized (arm 1: 888; arm 2: 887). Patient characteristics were well-balanced between the two arms: males 76.3%, median age 63 years (range: 34-88), squamous and large cell carcinomas 39.5%, stage I 68.1%, stage II 13.7%, stage III 18.3%, lobectomy or bilobectomy 86.6%, pre- and/or post-operative radiotherapy 8.7%, and pre- and/or post-operative chemotherapy 45%. Median follow-up was 8.7 yrs (95% CI: 8.5-9). OS was not significantly different between arms ($HR = 0.92$, 95% CI: 0.8-1.07; $p = 0.27$). Median OS was 8.2 yrs (95% CI: 7.4-9.6) and 10.3 yrs (95% CI: 8.5-not reached) in arms 1 and 2, respectively. Three-year disease-free survival rates were 63.3% (95%CI: 60.2%-66.5%), and 60.2% (95% CI: 57.0%-63.4%), respectively. Eight-year OS rates were 51.1% (95% CI: 47.2%-55.1%) and 55.6% (95% CI: 51.7%-59.4%) respectively.

Conclusions: The IFCT-0302 trial is the first randomized study of follow-up in resected NSCLC. The primary endpoint was not met. A longer follow-up is necessary not to miss a potential long-term OS benefit of CT-scan-based surveillance.

Clinical trial identification: NCT00198341

Legal entity responsible for the study: Intergroupe Francophone de Cancérologie Thoracique (IFCT)

Funding: Ministère de la Santé (PHRC), Fondation de France, Laboratoire Lilly

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ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

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NSCLC, EARLY STAGE

1274PD Analysis of immunoregulatory biomarkers in early stages of non-small cell lung cancer

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Background: The study of the tumour microenvironment is leading to a better understanding of the evasion of immune surveillance and the development of new therapies. This research focuses on the analysis of immunoregulatory genes as potential prognostic biomarkers in resectable non-small cell lung cancer (NSCLC).

Methods: The expression of 8 genes involved in immune-regulation (*PD-L1, PD-L2, IDO-1, IDO-2, ICOS-LG, CD5, CD6 and CD200*) was analysed by RTqPCR in 257 paired fresh frozen tumour and normal tissue samples of resected NSCLC. Relative expression was calculated by Pfaffl formulae using *ACTB, CDKN1B* and *GUSB* as endogenous controls. Non-parametric tests were used for correlations between clinicopathological and analytical variables and survival was assessed by Kaplan-Meier curves (long rank-test), considering significant $p < 0.05$.

Results: Patients median age was 64 years, 82% were males, 88% were former or current smokers, 47% were adenocarcinomas (ADC). Patients with higher expression of *CD5* and *IDO2* had a significant increase in overall survival (OS, 53.3 vs NR months, $p = 0.032$; 51.9 vs NR months, $p = 0.049$, respectively). A signature combining the expression of *CD5* and *IDO2* was able to better prognosticate survival (40.4 vs NR months, $p = 0.028$). The multivariate analysis (including clinico-pathological and analytical variables) showed that this signature has independent prognostic information OS (HR = 0.553 [0.344-0.887], $p = 0.016$). Moreover, in the subgroup of ADC increased expression of *CD5* and *IDO2* was associated with longer OS as well as increased relapse-free survival (RFS, 19.1 vs NR months, $p = 0.045$; 18.8 and 67.0 months, $p = 0.029$, respectively). The multivariate analysis established this gene signature as an independent prognostic biomarker for OS (HR = 0.380 [0.166-0.872]; $p = 0.026$) and RFS (HR = 0.288 [0.139-0.597]; $p = 0.002$).

Conclusions: The analyses revealed the prognostic value of *CD5* and *IDO2*, being their combination an independent prognostic marker in resectable NSCLC. Supported by grants from FEDER and PI12-02838 and PI15-00753 from ISCIII.

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1275PD Stemness characterization of tumorspheres from non-small cell lung cancer: Differential expression in CSC-related markers and signaling pathways

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Background: Treatment resistance and relapse have been associated to cancer stem cells (CSCs), a highly tumorigenic subpopulation of cells with self-renewal properties and the ability to grow forming tumorspheres in non-adherent conditions. The aim of this study was to isolate and characterize CSCs from lung cancer cell lines and tumor-tissue from resectable non-small cell lung cancer (NSCLC).

Methods: The study was performed on tumour cells from 8 resected NSCLC patients and 12 NSCLC cell lines grown in monolayer and as spheroids. The expression of 60 genes, including CSC-markers, pluripotency inducers, cell cycle regulators, invasion promoters and components of Notch, Wnt and Hedgehog pathways was analysed by RTqPCR. In addition, protein levels of CSC-markers (ALDH1A1, CD133, CD166, CD44 and EpCAM), pluripotency inducers (Nanog, Oct-4 and Sox2), Wnt components (Wnt3 and β-catenin) and Notch1 were assessed by western blot and immunofluorescence.

Results: Lung tumorspheres had significantly higher expression levels of CSC-related genes EPCAM1, CD44, ALDH1A1, CDKN1A, CCND1, and KLF4 compared to their paired-adherent cells. Similarly, epithelial to mesenquimal transition (EMT) inducer SNAI1 and integrins ITGA2, ITGA6 and ITGB1 were overexpressed in lungspheres. Notch pathway ligands, JAG1 and DLL4, receptors, NOTCH1, NOTCH2 and NOTCH3, and the effector factor HES1 showed increased expression in spheroids. In Wnt, higher expression levels of WNT3, CTNNB1 and GSK3B were found in tumorspheres. No significant differences were found for the rest of genes analyzed. Western blot and immunofluorescence analyses revealed that CD44, CD133, Sox2 and β-catenin were highly expressed in spheroids from cell lines and patients' samples. The expression of the rest of proteins evaluated differed among specimens.

Conclusions: Our results suggest four molecules which could act as markers for CSCs in NSCLC. Genes related to Notch and Wnt signaling pathways were more expressed in spheroids compared to the cells grown in adherence, suggesting that both pathways could be interesting targets against lung CSCs. Supported by grants RD12/0036/0025 from RTICC-FEDER, and PI12-02838 and PI15-00753 from ISCIII.

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1277PD A phase II randomized trial of adjuvant chemotherapy for the patients completely resected pathological stage IB (T > 5cm), II, IIIA non-small cell lung cancer comparing S-1 versus S-1 with cisplatin

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Background: Platinum-based combination chemotherapy is a standard postoperative adjuvant treatment for pathological stage II/III non-small cell lung cancer (NSCLC).

Oral S-1 therapy has been demonstrated to have a good efficacy with less toxicity for advanced NSCLC treatment. S-1 might be also useful in the adjuvant setting for surgical NSCLC.

Methods: We performed a phase II randomized open label multi-institutional study in surgical patients with pathological stage IB (T > 5 cm), II or III NSCLC (7th TNM classification), who underwent complete resection from 2009 to 2013. One hundred and thirty-nine patients were randomly assigned to two arms: S-1 80mg/m2 oral, day1 to 14, q3w, 1year (arm A, n = 70) or S-1 80mg/m2 oral day1 to 21, q5w + cisplatin 60mg/m2 day8, q5w, 4 courses, followed by S-1 80mg/m2 oral day1 to 14, q3w, total 1year (arm B, n = 69). The primary endpoint was the disease free survival (DFS) rate at 2 years and was evaluated using Bayesian method. Either treatment arm would deserve further study if the Bayesian posterior probability that the 2-year DFS rate would exceed a value of 40% were more than 0.85. The secondary endpoints were overall survival (OS), safety, and feasibility.

Results: The clinical characteristics of the patients were well balanced in terms of age, sex and pathological stage between the two arms. The DFS rate at 2 years was 51.4% (95% confidence interval [CI], 0.399–0.628) in arm A and 59.4% (95% CI, 0.476 – 0.702) in arm B. Both treatment arms met the primary endpoint: the probability of a DFS rate $\geq$ 40% at 2 years was over 0.97 in Arm and 1 in arm B. Neither DFS nor OS were significantly different (log-rank test; p = 0.1695 and p = 0.8684, respectively). No treatment-related deaths were observed in either treatment. The main G3/4 adverse events were appetite loss (arm A vs. arm B, 4.3% vs. 11.6%) and anemia (0% vs. 5.8%), which were not statistically different between the two arms. Treatment completion rate did not differ between the two arms (arm A vs. arm B: 45.7% [95% CI, 41.9–66.3%] vs. 43.5% [95% CI, 44.0–68.4%]).

Conclusions: Oral S-1 based adjuvant chemotherapy was feasible and promising for patients with completely resected NSCLC.

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Legal entity responsible for the study: academic group

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Disclosure: All authors have declared no conflicts of interest.

1278PD Major pathological response after preoperative chemotherapy as a surrogate marker of survival in early-stage non-small cell lung cancer: cohort of NATCH phase III trial

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Background: Randomized phase III NATCH trial in early-stage non-small cell lung cancer (NSCLC) patients (p) reported no statistically differences in disease-free survival (DFS) or overall survival (OS) with the addition of preoperative or adjuvant chemotherapy to surgery. In pre-operative arm, those p who achieved a complete response obtained a benefit in 5-year DFS rate (59% vs. 38%). Recently, major pathological response (MPR) to preoperative chemotherapy (10% or less of residual viable tumor after preoperative therapy) has reported as surrogate marker of OS. The aim of this study is to validate MPR as prognostic factor in a cohort of patients included the NATCH trial.

Methods: MPR was analysed in a whole cohort of 57 early-stage NSCLC p treated in the preoperative arm into NATCH trial from 2 institutions. OS according to MPR was analysed (long-rank test) in the whole population and by histologic subtype.

Results: In this cohort, median age was 67 years (47-78), 48 p (84%) were males, 26 p (46%) squamous subtype. By stage according to 6th TNM: 9 p (16%) stage IA, 35 p (61%) stage IB, 12 p (21%) stage IIB and 1 p (2%) stage IIIA. 95% p completed 3 cycles of preoperative treatment. Surgical procedures: 81% lobectomies, 14% pneumonectomies, 5% no surgery. 13 out of 57 p (22.8%) had MPR. In the whole population, there was an increase in 5-year OS among those patients with MPR compare to p without MPR (84.6% vs. 58.5%, p = 0.106). According to histological subtype, 5-year OS in squamous NSCLC p with MPR was significantly longer than in p without MPR (100% *vs.* 47.1%, p = 0.026), but not differences in OS in non-squamous were detected (66.7% *vs.* 66.7%, p = 0.586).

Conclusions: MPR is a prognostic value in squamous NSCLC p who receive preoperative chemotherapy. Validation in extended cohort merits further evaluation.

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Disclosure: All authors have declared no conflicts of interest.

1279P Factors predicting worse outcomes in patients with N0 lung adenocarcinoma of 3cm or smaller

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Background: The role of adjuvant chemotherapy for patients with stage I non-small cell lung cancer remains unknown. The prognostic value of histological subtypes in resected node-negative small-sized lung adenocarcinoma has not been widely investigated. This study investigated the prognostic factors in patients with node-negative lung adenocarcinoma of 3cm or smaller to find potential candidates for adjuvant chemotherapy.

Methods: A total of 746 patients with completely resected node-negative lung adenocarcinoma of 3cm or smaller were included in the study. Prognostic factors for overall survival or probability of freedom from recurrence (FFR) were investigated.

Results: The 5-year overall survival and recurrence-free rates were 86.8% and 84.8%, respectively. During follow-up, 59 (7.9%) patients developed recurrence. Univariate analysis showed that micropapillary/solid predominant group had significantly lower probability of FFR ($P = 0.001$) in node-negative lung adenocarcinoma of 3cm or smaller. Older age ($P = 0.007$), greater tumor size ($P = 0.006$), and micropapillary/solid predominant group ($P = 0.031$) had significantly lower probability of FFR in multivariate analysis.

Conclusions: The new adenocarcinoma classification has significant impact on recurrence in node-negative lung adenocarcinoma of 3cm or smaller. Patients with micropapillary/solid predominant pattern have significant higher risk for recurrence.

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1280P Regulatory variants in cancer-related pathway genes predict survival of patients with surgically resected non-small cell lung cancer

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Background: We conducted this study to identify genetic variants in cancer-related pathway genes which can predict prognosis of NSCLC patients after surgery, using a comprehensive list of regulatory single nucleotide polymorphisms (SNPs) prioritized by RegulomeDB.

Methods: A total of 509 potentially functional SNPs in cancer-related pathway genes selected from RegulomeDB were evaluated. These SNPs were analyzed in a discovery set (n = 354), and a replication study was performed in an independent set (n = 772). The association of the SNPs with overall survival (OS) and disease-free survival (DFS) were analyzed.

Results: In the discovery set, 76 SNPs were significantly associated with OS or DFS. Among the 76 SNPs, the association was consistently observed for 5 SNPs (*ERCC1* rs2298881C>A, *BRCA2* rs3092989G>A, *NELFE* rs440454C>T, *PPP2R4* rs2541164G>A, and *LTBP4* rs3786527G>A) in the validation set. In combined analysis, *ERCC1* rs2298881C>A, *BRCA2* rs3092989, *NELFE* rs440454C>T, and *PPP2R4* rs2541164G>A were significantly associated with OS and DFS (adjusted HR aHR for OS = 1.46, 0.62, 078, and 0.76, respectively; $P = 0.003$, 0.002, 0.007, and 0.003 respectively; and aHR for DFS = 1.27, 0.69, 0.86, and 0.82, respectively; $P = 0.02$, 0.002, 0.03, and 0.008, respectively). The *LTBP4* rs3786527G>A was significantly associated with better OS (aHR = 0.75; $P = 0.003$).

Conclusions: Our results suggest that five SNPs in the cancer-related pathway genes may be useful for the prediction of the prognosis in patients with surgically resected NSCLC.

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1281P Relevance between PD-L1 and radiological invasiveness in pathological stage I lung adenocarcinoma

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Background: Programmed death-ligand 1 (PD-L1) was reported to predict the response of immunotherapy; however, the association between PD-L1 expression and radiological/pathological features has yet to be elucidated.

Methods: A total of 292 patients with resected pathological stage I adenocarcinoma were analyzed for PD-L1 expression by immunohistochemistry and evaluated to determine the association between PD-L1 expression and the radiological/pathological invasiveness. Specifically, the radiological invasiveness and noninvasiveness were determined based on the consolidation/tumor (C/T) ratio, with a cut-off value of 0.25 by thin-section computed tomography.

Results: Among 292 patients, 47 (16.1%) were positive for PD-L1 expression; the remaining 245 patients (83.9%) were negative for PD-L1 expression. Fisher's exact test demonstrated that PD-L1 expression was significantly associated with a higher C/T ratio (P=0.029) and higher maximum standardized uptake value (SUVmax; P=0.004). The mean values of C/T ratio and SUVmax in patients with and without PD-L1 expression were 0.845±0.052 and 7.241±0.795, and 0.607±0.023 and 3.60±0.364, respectively (P<0.001 and P<0.001, respectively). Among 47 adenocarcinomas harboring PD-L1 expression, the frequencies of PD-L1 expression for C/T ratios of 0, 0.1-0.25, 0.26-0.5 and ≥0.51 were 6.4%, 2.1%, 4.3% and 87.2%, respectively (P=0.007). Pathologically, PD-L1 was identified exclusively only in more invasive subtypes, not in less invasive ones, such as atypical adenomatous hyperplasia, adenocarcinoma in situ, minimally invasive adenocarcinoma, and lepidic predominant ones (P<0.001).

Conclusions: PD-L1 expression was significantly associated with radiological/pathological invasive adenocarcinomas. This study provides the first evidence of the radiological/pathological invasiveness in resected pathological stage I adenocarcinoma with PD-L1 expression.

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Disclosure: All authors have declared no conflicts of interest.

1282P Characterization of cancer stem cell and immune microenvironment interactions in non-small cell lung cancer (NSCLC)

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Background: Lung cancer stem cells (CSCs) are a small subpopulation of cells with self-renewal, tumorigenic properties and the ability to grow forming tumourspheres in non-adherent conditions. CSCs in non-small cell lung cancer (NSCLC) are targets poorly recognized by the immune surveillance system given that they favour an immunosuppressive microenvironment. The aim of this work was to compare the release of cytokine between monolayer cells and tumourspheres.

Methods: The study was performed on medium supernatant of cells from two NSCLC tumour patients (patient 1 and patient 2) samples and ten cell lines (A549, H1650, H460, H23, H358, H2228, HCC827, PC9, H1993, and SW900) grown in monolayer and tumourspheres at 3 different densities (10^4, $5{\cdot}10^5$ and 10^5 cells/ml). We analysed four soluble factors with immunosuppressive (IL-4, IL-10), and immunoregulatory (IL-6, IL-8) capacity through sensitivity bead-based multiplex assay using the Millipore kit and the Luminex 100/200.

Results: All human tumour cell lines and primary cells secreted detectable levels of IL-6 and IL-8. In contrast, IL-10 and IL-4 levels were below detectable range (<1.83 and <1.46 pg/ml, respectively) for most of these cell lines and NSCLC tumour samples. We have observed differences between levels of IL-6 and IL-8 secreted by adherent cells and tumourspheres and differences between samples (Table).

Conclusions: Our preliminary results suggest that cells grown in adherence show increased levels of IL-6 compared to lung-tumourspheres. The next step is the expansion of the cohort to obtain significant results.

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Disclosure: All authors have declared no conflicts of interest.

1283P Non-invasive detection of lung cancer by identifying copy number aberrations in circulating cell-free DNA with next generation sequencing to aid early detection

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Background: Population stratification with molecular biomarkers could improve the cost-benefit of lung cancer screening programmes and reduce false positives. We aim to establish that somatic copy number aberrations (SCNA) are detected in circulating cell-free DNA (cfDNA) of lung cancer cases. We hypothesise that the number and magnitude of SCNA might also serve as a discriminative test to aid early lung cancer detection.

Methods: Standard protocols were followed to process matched cfDNA and lymphocyte DNA for 51 untreated lung cancer cases, 30 high risk controls and 10 low risk controls. Low coverage DNA sequencing was carried out on the Illumina Hiseq 2500 and read copy number profiles were established with the software CNAnorm. A genomic instability score was evaluated by defining the area under the receiver operating characteristic curve (AUROC).

Results: The median coverage of the genome for cfDNA was 0.49X (range 0.2X-0.63X). There was no significant difference between the median whole genome copy number aberration (CNA) score for early stage lung cancer and high risk controls, 398 (117-15373) vs 252 (149-7122) p = 0.25. The AUROC was 0.60 (95% CI 0.47-0.78) for early stage cancer (N = 21) and high risk controls compared to an AUROC of 0.74 (95% CI

Table: 1282P Differences in the secretion of IL-6 and IL-8 in adherent cells and tumourspheres by multiplex analysis. Detection range of IL-6 (0.17-1750.12 pg/ml). Detection range of IL-8(0.28-2273.3 pg/ml)

Samples	pg/ml x 10^5 cells IL-6		pg/ml x $\cdot 10^5$ cells IL-8	
	Adherent cells	Tumourspheres	Adherent cells	Tumourspheres
A549	<0.17	1.3	130.1	158.2
H2228	1750,11	>1750.12	>2273.3	172.80
HCC827	348.2	>1750.12	2177.4	>2273.3
H358	10.9	27.8	1774.8	>2273.3
H1993	34.4	2.2	658.2	479.3
PC9	144.4	5.4	597.2	321.9
SW900	121.7	5.4	1006	225.2
H460	359.8	227.8	1298.8	2201.3
H23	3.7	2.8	407.8	1290.8
H1650	995.9	352.2	30.2	50.3
Patient 1	17.4	0.6	>2273.3	30.0
Patient 2	>1750.12	>1750.12	>2273.3	>2273.3

0.63-0.85) for all lung cancer cases. The CNA score was a significant prognostic factor in univariable (HR 1.22 (95% CI 1.05-1.42 p = 0.008) but not multivariable analyses (HR 0.91 (95% CI 0.73-1.15 p = 0.45).

Conclusions: Our preliminary results demonstrate non-invasive detection of tumour derived copy number alterations with low coverage whole genome sequencing. The CNA score is not recommended as a stand-alone test to aid early lung cancer detection.

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Disclosure: All authors have declared no conflicts of interest.

1284P HOXA-related long non-coding RNAs impact prognosis in early stage NSCLC patients

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Background: HOX genes, grouped in four clusters in humans (HOXA-D), encode for transcription factors that are master regulators of embryonic development and oncogenesis. HOXA cluster, located in chromosome 7, play a critical role in the patterning of tissues with mesodermal components such as lungs. Long non-coding RNAs (lncRNAs) are especially abundant in the HOXA cluster (HOXA10-AS, HOXAS2, HOXAS3, HOXA11-AS, HOTAIRM1 and HOTTIP). We aimed to evaluate the prognostic role of HOXA-related lncRNAs in early stage non-small cell lung cancer (NSCLC).

Methods: 100 early stage NSCLC patients resected in our center from June 2007 to November 2013 were studied. Patient characteristics: median age, 65 (32-84); 78% males; 74% stage I; 56% ADK; 23% received adjuvant treatment. With a mean follow-up of 28.7 months, 31% relapsed. As validation data set 200 NSCLC patients from TCGA Research Network were used (RNAseq data). Only stage I-II TCGA samples without prior malignancy or synchronous cancer that not received neoadjuvant treatment were included. Statistical analysis was performed using R and TANRIC.

Results: HOTTIP and HOXA11AS impacted prognosis in our cohort of patients. HOTTIP was expressed in all samples and patients with high levels of HOTTIP had shorter TTR (78.3 vs 58 months; p = 0.048) and shorter OS (81.2 vs 61 months; p = 0.023). HOTTIP was overexpressed in SCC (p = 0.007) and in smokers (p = 0.018). HOXA11AS was expressed only in 9% of patients but the patients expressing HOXA11AS had shorter TTR (73.5 vs 32 months; p = 0.002). In the multivariate analysis HOXA11AS emerged as an independent prognostic marker for TTR (OR: 3.13, 95%CI: 1.3-7.3; p = 0.009), while HOTTIP (OR: 2.357, 95%CI: 1.1-5.2; p = 0.036) and age>65 (p = 0.022) for OS. In the validation data set HOXA11AS was validated as prognostic marker (p = 0.019). HOXA11AS expression correlated positively with development genes HOXA11, HOXA13, HOXA10, HOXA9, HOXA3, FOXD1, ZIC5 and miR-196b (HOXA cluster miRNA) and negatively with surfactant metabolism genes SFTPB and NAPSA or let-7a(p < 0.001). Interestingly, the high expression was associated to patients harboring RTN1 mutations (p < 0.0001).

Conclusions: HOXA11AS expression in early stage NSCLC patients is a high-risk relapse marker.

Legal entity responsible for the study: University of Barcelona, Barcelona, Spain

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1285P Association between polymorphisms in microRNA target sites and survival in early-stage non-small cell lung cancer

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Background: MicroRNAs (miRNAs) are small non-coding RNAs that function in regulation of gene expression. Recent studies have also suggested that single nucleotide polymorphisms (SNPs) located in miRNA target sites can influence the prognosis of diverse human cancers, including lung cancer. This study was conducted to evaluate the associations between single nucleotide polymorphisms (SNPs) in miRNA target sites using CLASH data and the survival outcomes of early-stage non-small cell lung cancer (NSCLC) patients.

Methods: 100 potentially functional polymorphisms were selected based on cancer-related miRNA target site in PolymiRTS database 3.0(http://compbio.uthsc.edu/miRSNP), CLASH data, and CancerGenes database (http://cbio.mskcc.org/cancergenes). All polymorphisms were genotyped using SEQUENOM's MassARRAY® iPLEX assay according to instructions of the manufacturer. The genotype association with overall survival (OS) and disease-free survival (DFS) in 782 patients with NSCLC who underwent curative surgical resection were analyzed.

Results: Among the 100 SNPs studied, two SNPs showed significant association with survival outcomes. Patients carrying the *POLR2A* rs2071504TT or CT genotypes showed significantly lower overall survival and disease-free survival than those with the *POLR2A* rs2071504CC genotype (HR = 1.42, 95% CI = 1.08–1.88, *P* = 0.01 and HR = 1.34, 95% CI = 1.08–1.67, P = 0.01, respectively). The *NR2F6* rs2288539C>T variant was found to be significantly associated with higher overall survival under the recessive model (HR = 0.13, 95% CI = 0.02–0.90, *P* = 0.04).

Conclusions: Our findings suggest that the *POLR2A* rs2071504C>T and *NR2F6* rs2288539C>T can influence the prognosis of early-stage NSCLC patients.

Legal entity responsible for the study: Jae Yong Park

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1286TiP Neo-adjuvant chemo/immunotherapy for the treatment of resectable stage IIIA non-small cell lung cancer (NSCLC): A phase II multicenter exploratory study" NADIM trial

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Background: Lung cancer is the primary cause of cancer mortality in western countries. The cure is unlikely in patients with NSCLC and locally advanced stage who are not surgical candidates, with a 3-year survival rate of 27% in those patients receiving chemotherapy and concomitant radiotherapy. On the contrary, in localized stages (stage I, II, IIIA) with surgical resection and cytostatic therapy, a survival of 5 years of 51% is achieved. Currently, there is no consensus on the best standard treatment: the surgical management of stage IIIA NSCLC remains highly controversial and most patients with stage IIIB disease are generally considered inoperable. Since distant metastases remain the major site of failure, it is likely that more effective cytotoxic or other anti-tumor agents will be required. Chemotherapy stimulates an immune response against tumors, which may facilitate immunotherapy anticancer activity. Evidence of synergy between chemotherapy and immunotherapy was shown in several studies.

Trial design: Phase II, single-arm, open-label multicenter study that assesses feasibility, safety and efficacy of combined neoadjuvant therapy with Nivolumab 360 mg + Paclitaxel 200mg/m2 + Carboplatin AUC 6 Q3W, three cycles, in resectable stage IIIA NSCLC patients followed by adjuvant treatment for 1 year with Nivolumab 240 mg Q2W for 4 months and Nivolumab 480mg Q4W for 8 months. The primary endpoint will be Progression Free Survival at 24 months from diagnosis and to assess the efficacy of the combination. The secondary endpoints will be time to progression and overall survival at 3 years, response rate, toxicity profile of the combination, the down-staging rate and complete resection rate. Also, surgical outcome and complications will be assessed. Perform correlatives studies with the objectives of exploring the expression of other biomarkers, such as PD-L1, in tumor tissue, free DNA and circulating tumor cells in liquid biopsy. Describe whether PD-L1 expression is a predictive biomarker for ORR, describe PFS in PD-L1 + (≥1%) population and report imaging response versus pathological response rate.

Clinical trial identification: EudraCT Number: 2016-003732-20

Legal entity responsible for the study: Spanish Lung Cancer Group

Funding: Bristol-Myers Squibb

Disclosure: All authors have declared no conflicts of interest.

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NSCLC, LOCALLY ADVANCED

1287PD Preoperative chemotherapy and radiotherapy concomitant to cetuximab in stage IIIB NSCLC: A multicenter phase II SAKK

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Background: Stage IIIB NSCLC treatment is definitive chemo-radiotherapy (CRT). In our SAKK 16/01 trial, neoadjuvant chemotherapy (CT) followed by neoadjuvant accelerated radiotherapy (RT) and surgery showed a median survival of 28.7 months (mos) in selected stage IIIB patients (pts). These promising results are the rationale for the current trimodality concept, introducing concomitant cetuximab (CET) to neoadjuvant CRT.

Methods: Pts with pathologically proven resectable stage IIIB (T4N0-3M0 or T1-4N3M0, 6th TNM) NSCLC, PS 0-1, and adequate organ function were treated with 3 cycles of neoadjuvant CT (cisplatin 100 mg/m^2 and docetaxel 85 mg/m^2 d1, q3w) followed by accelerated concomitant boost RT (44 Gy in 22 fractions in 3 weeks), both with concomitant weekly CET (250mg/m^2) and subsequent surgery. The primary endpoint was progression-free survival (PFS) at 1 year (yr).

Results: 69 pts were treated in 11 Swiss centers. 2/3 were men, median age was 60 yrs. Histology was squamous in 41% and adenocarcinoma in 49%, with T4 disease in 61%, N3 in 46% and both in 7%. A median relative total dose intensity of 99% of CT and 91% of CET was delivered. Per protocol RT was delivered to 95% of pts. 57 (83%) pts underwent surgery, with complete resection (R0) in 74% and a postoperative 30d mortality of 4%. Response rate after CT-immunotherapy was 57% and 64% after CRT-immunotherapy (CRT-I). Major pathologic response was found in 36% of the resected pts. 1-yr PFS based on Kaplan-Meier estimation was 50% (95% CI: 37%-62%). Median PFS was 12 mos (95% CI: 9-16), median OS was 21 mos (95% CI: 14-25), with a 2 and 3-yr survival of 41% and 30%, respectively.

Conclusions: This is one of the largest prospective phase II trials to evaluate the role of induction CRT-I and surgery in resectable stage IIIB disease, and the first to associate concurrent CET to the neoadjuvant strategy. Trial treatment is feasible with excellent adherence to the protocol and promising clinical and pathological response rates, PFS and OS, supporting an aggressive approach including surgery in selected IIIB pts. As compared to our previous SAKK 16/01 experience, the addition of CET does not improve the outcome of this group of locally advanced NSCLC pts.

Clinical trial identification: SAKK 16/08, NCT01059188, original version dated: 24.08.2009, including amendments: 04.07.2013.

Legal entity responsible for the study: Swiss Group for Clinical Cancer Research (SAKK)

Funding: Merck Serono

Disclosure: All authors have declared no conflicts of interest.

1288PD Randomized phase ii trial comparing chemoradiotherapy with chemotherapy for completely resected unsuspected N2-positive non-small cell lung cancer

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Background: We investigated whether concurrent chemoradiotherapy (CCRT) would increase survival in patients with completely resected unsuspected N2-positive non-small cell lung cancer (NSCLC), compared with adjuvant chemotherapy alone.

Methods: Eligible patients were randomly assigned (1:1 ratio) to either the CCRT arm or the chemotherapy arm. In the CCRT arm, patients received concurrent thoracic radiotherapy (50 Gy in 25 fractions) with five cycles of weekly paclitaxel (50 mg/m^2) and cisplatin (25 mg/m^2), followed by two additional cycles of paclitaxel (175 mg/m^2) plus cisplatin (80 mg/m^2) at three-week intervals. In the chemotherapy arm, patients received four cycles of adjuvant paclitaxel (175 mg/m^2) and carboplatin (AUC 5.5) every three weeks. The primary endpoint was disease-free survival.

Results: We enrolled and analyzed 101 patients. The median disease-free survival of the CCRT arm was 24.7 months, which was not significantly different from that of the chemotherapy arm (21.9 months; hazard ratio [HR] 0.94, 95% CI: 0.58–1.52, P = 0.40). There was no difference in overall survival (CCRT: 74.3 months, chemotherapy: 83.5 months, HR: 1.33, 95% CI: 0.71–2.49). Subgroup analysis showed chemotherapy alone increased overall survival in never-smokers and multi-station N2-positive patients. The pattern of disease recurrence was similar between the two arms.

Conclusions: There was no survival benefit from adjuvant CCRT compared with platinum-based chemotherapy alone for completely resected unsuspected N2-positive NSCLC. However, the role of sequential radiotherapy administered after adjuvant chemotherapy is being evaluated, and further study is needed to evaluate the optimal radiotherapy approach for completely resected N2-positive NSCLC.

Clinical trial identification: (NCT01066234)

Legal entity responsible for the study: Keunchil Park

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1289PD Clinical course in patients with stage III non-small cell lung cancer and interstitial lung disease treated with chemoradiotherapy: a retrospective analysis in a single institute

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Background: Patients with non-small cell lung cancer (NSCLC) and interstitial lung disease (ILD) are often excluded from clinical trials because they are considered to be at high risk for acute exacerbation (AE) of ILD triggered by radiotherapy. Therefore, data on the clinical course in these patients are limited. We examined the relationship between chemoradiotherapy (CRT) and occurrence of AE of ILD as well as the clinical course in these patients at our institution.

Methods: A retrospective analysis was performed on 37 patients with stage III NSCLC and ILD treated with first-line CRT in a clinical setting between January 2009 and December 2014 at our institution.

Results: Patient characteristics are shown in Table 1. Patients treated with CRT had milder ILD than those treated with chemotherapy alone. Eighteen patients treated with CRT received corticosteroids for the treatment of AE of ILD. Univariate analysis revealed that the risk factors for AE of ILD were ILD classification, smoking history, and V20. In multivariate logistic regression analysis, the independent risk factor for AE of ILD was ILD classification. AE of ILD occurred in nine (82%) patients with usual interstitial pneumonia (UIP) pattern and in nine (35%) with non-UIP pattern. Median overall survival (mOS) was 34.6 months. Univariate analysis and multivariate logistic regression analysis revealed that the prognostic factor for patients with stage III NSCLC and ILD treated with CRT was ILD classification. mOS was 10.9 and 43.0 months in UIP and non-UIP patterns, respectively.

Conclusions: In conclusion, this retrospective analysis suggests that ILD classification (UIP or non-UIP) is associated with the occurrence of AE of ILD and prognosis in patients treated with first-line CRT.

Table: 1289PD

First-line treatment Variable	Chemoradiotherapy (N = 37)	Radiotherapy (N = 17)	Chemotherapy (N = 25)
Age, median (range)	73 (52–85)	80 (59–89)	69 (58–81)
Sex, male/female	32/5	15/2	21/4
PS, 0/1/2	15/22/0	6/7/4	10/15/0
Clinical staging (TNM classification, 7th edition), IIIA/IIIB	20/17	8/9	10/15
Smoking history, yes/no	33/4	16/1	24/1
Histology, squamous/non-squamous	19/18	7/10	13/12
ILD classification, UIP/non-UIP	11/26	6/11	16/9
%VC, median (range)	96 (59–129)	86 (62–112)	85 (64–121)
V20, median (range)	27 (12–35)	26 (14–36)	
Lung volume loss or honeycombing	4	4	13

Clinical trial identification: The study protocol was approved by the Institutional Review board of Shizuoka Cancer Center (28-J167-28-1-3).

Legal entity responsible for the study: Haruki Kobayashi

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1290P DNA repair gene expression in bronchial washing fluid as new molecular tool for clinical outcome decision

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Background: Platinum-based drugs (cisplatin, etc.) are used as a first-line therapy for NSCLC patients. However, such treatment is not effective for all patients. Biomarkers that could predict efficiency of the platinum-based treatment should be identified. Aim: To evaluate whether the response to treatment of NSCLC patients is based on *ERCC1* and *RRM1* gene expression in bronchial washing fluid.

Methods: 70 patients with a first-time diagnosed NSCLC receiving Cisplatin+Etoposid were involved in the study. RNA was extracted from bronchial washing fluid using "RNeasy Plus Mini Kit" (*QIAGEN*, Germany). The analysis of *ERCC1* and *RRM1* 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. The prognostic significance was assessed by the Cox proportional hazards regression model.

Results: Statistically significant differences were found between *ERCC1* expression and tumour differentiation grade, *RRM1* expression and disease stage and lymph node status. *ERCC1* expression was associated with NSCLC patient progression-free survival (PFS) rate depending on gender, disease stage, response to treatment. Patients from high *ERCC1* expression group had 7.6 months longer survival than patients from low expression group. *RRM1* expression was associated with NSCLC patients PFS rates depending on gender, age, tumour histology and differentiation grade. Patients from low *RRM1* expression group had 7.9 months longer survival than those from high expression group. Multivariate analysis of factors influencing PFS rate showed that disease stage ($p = 0.01$), tumor differentiation grade ($p = 0.009$), response to treatment ($p = 0.02$) and RRM1 expression ($p = 0.001$) were independent prognostic factors of NSCLC patients PFS.

Conclusions: *ERCC1* and *RRM1* genes may influence platinum-based chemotherapy treatment of NSCLC patients. In order to improve the effectiveness of treatment it is appropriate to identify *RRM1* expression changes in the bronchial washing fluid. Therefore, NSCLC patients with high *RRM1* expression should be actively followed-up because of quicker disease progression.

Clinical trial identification: Lithuanian Bioethics Committee No. 158200-09-381-104

Legal entity responsible for the study: National Cancer Institute

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1291P Diagnosis and monitoring of non-small cell ung cancer patients by next generation sequencing and droplet digital PCR on circulating tumor DNA

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Background: About 80% to 85% of lung cancers are non-small cell lung cancer (NSCLC). EGFR tyrosine kinase inhibitors as well as several other targeting molecules have been demonstrated to be effective in treating patients with activating mutations. We investigated the use of circulating tumor DNA (ctDNA) and high sensitive detection techniques for mutational profiling to improve the diagnosis and monitoring of NSCLC patients.

Methods: ctDNA was extracted from plasma using the QIAamp Circulating Nucleic Acid kit (Qiagen). A custom panel was designed to cover EGFR, KRAS, NRAS, BRAF, PIK3CA, DDR2, AKT1, PTEN, MEK1 and ERBB2 hotspot mutations. Libraries, constructed according to the AmpliSeq protocol, were sequenced on the semiconductor Ion Torrent S5XL platform. The presence of the EGFR T790M mutation was also assessed by a digital PCR assay.

Results: A total of 120 patients from 30 Belgian institutions were enrolled in this prospective study. The majority of patients presented with stage IV adenocarcinoma and progression. Forty-six (46) patients had a mutation detected on a former biopsy: EGFR exon 19 (26), EGFR exon 21 (8), KRAS (10), PIK3CA (1) and ERBB2 (1). Among those patients, 28 (61%) harbored the same mutation when their ctDNA was sequenced with our NGS panel: EGFR exon 19 (15), EGFR exon 21 (6), KRAS (5), PIK3CA (1) and ERBB2 (1). For 7 patients, for which no mutation had not been previously detected, 4 EGFR, 2 KRAS and 1 NRAS mutations were found after ctDNA analysis. As far as the ddPCR detection of EGFR T790M was concerned, the mutation was detected on 7 (21%) of the 34 patients presenting EGFR mutations in their prior biopsy (5 in exon 19 and 2 in exon 21). Patients with acquired T790M mutation were previously treated by Afatinib (3), Erlotinib (2) or Gefitinib (1).

Conclusions: Our results indicate that ctDNA can be an alternative and noninvasive source of tumor DNA, a surrogate to classical biopsies, particularly when access to tumor tissue is limited. NGS and ddPCR assays are sensitive enough to promote a clinical translation of ctDNA analysis into disease management and therapeutic decision. Supported by a grant from Boehringer Ingelheim.

Legal entity responsible for the study: Institut de Pathologie et de Génétique

Funding: Boehringer Ingelheim Institut de Pathologie et de Génétique

Disclosure: All authors have declared no conflicts of interest.

1292P Safety data from randomized phase II study of cisplatin (CDDP)+S-1 versus CDDP+pemetrexed (PEM) combined with thoracic radiotherapy (TRT) for locally advanced non-squamous (non-sq) non-small cell lung cancer (NSCLC): SPECTRA study

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Background: Both CDDP+S-1 and CDDP+PEM could be given at full systemic doses with TRT in locally advanced NSCLC, and CDDP+PEM is one of the standard chemotherapy regimens in patients with advanced non-sq NSCLC. This multicenter, randomized, open-label, phase II study (SPECTRA) compared the efficacy and safety of the two above-mentioned promising regimens combined with TRT in patients with unresectable locally advanced non-sq NSCLC.

Methods: Patients were randomly assigned to receive CDDP+S-1 (CDDP 60mg/m2, d1, and S-1 80mg/m2, d1-14, q4w, up to 4 cycles) or CDDP+PEM (CDDP 75mg/m2, d1, and PEM 500mg/m2, d1, q3w, up to 4 cycles) combined with TRT 60Gy in 30 fractions. The primary endpoint was 2-year progression-free survival (PFS) rate. The sample size was set at 100 patients.

Results: Between Jan 2013 and Oct 2016, 102 patients were enrolled in this study from 9 institutions in Japan. All 102 patients were eligible and assessable, of whom 52 were assigned to CDDP+S-1 and 50 to CDDP+PEM. Baseline characteristics were similar (CDDP+S-1/CDDP+PEM): median age (range) 64.5 (39-73)/63.5 (32-74) years; women, n = 17 (33%)/n=17 (34%); stage IIIB, n = 21 (40%)/n=20 (40%); ECOG PS of 1, n = 14 (27%)/n=14 (28%); never smoker, n = 12 (23%)/n=12 (24%); and adenocarcinoma, n = 47(90%)/n=45(90%). Completion rate of TRT (60Gy) and chemotherapy (4 cycles) was 92%/98% and 73%/86%, respectively. Response rate was 60%/64%. Grade 3 toxicities included febrile neutropenia (12%/2%), anorexia (8%/16%), diarrhea (8%/0%), esophagitis (6%/8%), pneumonia (4%/4%), neutropenia (35%/50%), anemia (8%/12%), thrombocytopenia (4%/6%), and hyponatremia (12%/12%). Grade 2 radiation pneumonitis was observed in 8 (15%)/2 (4%) patients. No treatment-related death was observed. The data on PFS and overall survival is immature.

Conclusions: Response rate was similar between two arms. Toxicities were tolerable and manageable in both arms; however febrile neutropenia was more frequently observed in the CDDP+S-1 arm. Survival data will be analyzed in late 2018.

Clinical trial identification: UMIN000009914 (release date: 31/Jan/2013)

Legal entity responsible for the study: Yuichiro Ohe

Funding: Japan Agency for Medical Research and Development

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1293P Preliminar analysis of the Spanish Lung Cancer Group (SLCG) phase II trial of concurrent chemo-radiotherapy (CT-RT) with cisplatin (P) plus metronomic oral vinorelbine (mOV) for unresectable locally advanced non-small cell lung cancer (LA-NSCLC): NORA trial (GECP 15/02)

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Background: CT-RT is the standard treatment for unresectable LA-NSCLC. P plus vinorelbine is widely used. Metronomic CT is a frequent administration of low doses of CT. mOV has shown good efficacy and improved safety, and could improve the RT effect. Our goal is to evaluate the efficacy and safety of P-mOV with radical RT in patients (pts) with LA-NSCLC.

Methods: Pts aged 18-75 years with histologically proven untreated and unresectable LA-NSCLC, adequate bone marrow, hepatic & renal function, ECOG PS0-1, received P 80mg/m^2 D1 every 3 weeks combined with mOV 50mg/day on days D1, 3 & 5/weekly, 2 cycles (cy) as induction; patients without progression received 2 more cy of P at the same dose with mOV 30mg/day on D1, 3 & 5/weekly, concurrently with RT (66Gy in 6.5weeks). Primary endpoint was progression-free survival (PFS) by RECIST v1.1; secondary endpoints were: overall response rate, overall survival and safety profile. To guarantee an overall type-1 α error no greater than 0.05 and a type II (β) error 0.1 for PFS, a sample size of 67 pts was planned.

Results: Since May 2016, 58 pts have been recruited. Fifty-three pts have been included in the analysis. Pt characteristics: Male 72%; median age 63 (range 33-75); PS 0/1 62/48%; smokers 48%; adenocarcinoma/squamous 43.4/35.9%; stage IIIA/B 35.9/58.5%. Hematological G3-4 toxicities: neutropenia 18.9%; anemia 3.8%; febrile neutropenia 7.5%. Non-hematological G3-4 toxicities: esophagitis 1.9%; infection without neutropenia 1.9%; dyspnea 3.8%; thromboembolism 3.8%. No treatment-related deaths were reported.

Conclusions: mOV-P administered with RT has a manageable safety profile. Based on this, accrual is ongoing.

Clinical trial identification: EudraCT 2015-003312-21.

Legal entity responsible for the study: Spanish Lung Cancer Group (SLCG)

Funding: Spanish Lung Cancer Group (SLCG)

Disclosure: All authors have declared no conflicts of interest.

1294P Real world data of practice patterns and outcomes for pemetrexed plus platinum as neoadjuvant chemotherapy in adenocarcinomas of lung from a tertiary cancer center of India: Looking beyond the usual paradigm

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Background: Neoadjuvant chemotherapy (NACT) is the standard of care in non-small cell lung cancers (NSCLC) with locally advanced N2 disease. There is scarcity of data for pemetrexed-platinum regimen as NACT. Also, aside from N2 disease, role of NACT in locally advanced NSCLCs for tumor downstaging is unclear.

Methods: Nonmetastatic adenocarcinomas of lung treated with pemetrexed-platinum based NACT were analysed. The patients with locoregionally advanced N2 disease and those who were borderline candidates for upfront definitive treatment were planned for NACT after discussion in a multidisciplinary clinic. Total 4 cycles of 3-weekly pemetrexed and platinum were delivered in combined neoadjuvant and adjuvant setting. Response assessment was done using RECIST criteria. Progression free (PFS) and overall survival (OS) were calculated using Kaplan Meier method.

Results: Out of 114 evaluable patients, 99 patients received NACT with pemetrexed-platinum. Most common indication for NACT was N2 disease at baseline (46.4%). Objective response rate was 38.2% (95% CI: 23%-53%) including two complete and 34 partial responses. 12.7% patients had progressive disease on NACT. Median PFS was 15 months (95% CI 11.6-18.4) and median OS was 22 months (95% CI 15.6-28.3) at a median follow-up of 16 months. There was a significant improvement in the OS of patients undergoing definitive therapy versus no definitive therapy (median OS 25 months [95% CI 19.4-30.3] vs 12 months [95% CI 3.2-20.3] respectively; p = 0.047, HR 1.6). Amongst patients who could not undergo definitive CTRT upfront due to dosimetric constraints (n = 36), 26 (72.2%) patients finally underwent CTRT after NACT. Those patients who were not able to undergo definitive CTRT had median PFS of 5 months [95% CI 2.1-7.9] versus 10 months [95% CI 3.8-16.1] in those who were made amenable to definitive CTRT post NACT; p = 0.018.

Conclusions: Pemetrexed-platinum based NACT appears to be an effective option and many borderline cases where upfront definitive therapy is not feasible may become amenable to the same after incorporation of NACT.

Clinical trial identification: Clinical Trials Registry India (registration number: CTRI/2013/01/003335)

Legal entity responsible for the study: Tata Memorial Hospital, Mumbai

Funding: None

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NSCLC, METASTATIC

1295O Blood-based biomarkers for cancer immunotherapy: Tumor mutational burden in blood (bTMB) is associated with improved atezolizumab (atezo) efficacy in 2L+ NSCLC (POPLAR and OAK)

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Background: Atezo (anti–PD-L1) was FDA approved for 2L+ NSCLC based on results from the randomized OAK and POPLAR trials, with atezo showing superior efficacy vs docetaxel (doc). We previously showed that TMB in tissue correlates with atezo efficacy in 1L+ NSCLC. To address the significant challenge of consistently obtaining sufficient tumor tissue for molecular testing, we developed a novel blood-based assay to measure bTMB. Here we analyzed plasma samples from OAK and POPLAR with the bTMB assay to correlate bTMB with atezo clinical activity.

Methods: The biomarker evaluable population (BEP) included 211 pts in POPLAR (ITT=287) and 583 pts in OAK (excludes pts with known *EGFR*/*ALK* mutations; ITT=850), with blood samples available for targeted genomic sequencing. The bTMB assay interrogates single nucleotide variants (SNVs) in 394 genes from cell-free DNA in plasma and reports a score based on the number of high-confidence SNVs identified. The BEP was grouped by bTMB cut points based on the minimum number of SNVs present.

Results: In POPLAR, improved PFS and OS HRs with atezo vs doc were observed at a range of bTMB cut points compared with the ITT and BEP. In OAK, PFS benefit with atezo vs doc was observed at bTMB cut points $\geq$ 10 compared with BEP. (Table) Importantly, bTMB did not correlate with PD-L1 expression (SP142 or 22C3).

Conclusions: These exploratory analyses represent the first demonstration of a novel blood-based assay measuring bTMB that may predict atezo clinical efficacy in 2L+ NSCLC. Thus, the bTMB assay may provide a non-invasive biomarker to identify pts who may derive clinical benefit from single agent checkpoint inhibition. Prospective studies using bTMB are currently ongoing in pts with 1L NSCLC (B-F1RST/BFAST).

Table: 1295O Clinical efficacy of atezo vs doc in bTMB subgroups

	POPLAR study		
	ITT (N = 287)		**BEP (N = 211)**
OS HR (95% CI)	0.73 (0.53, 0.99)		0.68 (0.50, 0.93)
PFS HR (95% CI)	0.94 (0.72, 1.23)		0.90 (0.68, 1.20)
bTMB subgroup	**$\geq$ 10**	**$\geq$ 16**	**$\geq$ 20**
No. of patients	96	63	42
OS HR	0.59	0.56	0.51
PFS HR	0.68	0.57	0.58
	OAK study		
	ITT (N = 850)		**BEP (N = 583)**
OS HR (95% CI)	0.73 (0.62, 0.87)		0.64 (0.53, 0.77)
PFS HR (95% CI)	0.95 (0.82, 1.10)		0.87 (0.73, 1.04)
bTMB subgroup	**$\geq$ 10**	**$\geq$ 16**	**$\geq$ 20**
No. of patients	251	158	105
OS HR	0.69	0.64	0.65
PFS HR	0.73	0.65	0.61

BEP, biomarker-evaluable population; bTMB, tumor mutational burden in blood; ITT, intention to treat.

Clinical trial identification: NCT02008227; NCT01903993

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

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1296O Clinical efficacy of atezolizumab (Atezo) in PD-L1 subgroups defined by SP142 and 22C3 IHC assays in 2L+ NSCLC: Results from the randomized OAK study

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Background: In the Phase III OAK trial, patients (pts) with previously treated advanced NSCLC had improved median overall survival (OS) with atezo vs docetaxel (doc), regardless of PD-L1 expression (per VENTANA PD-L1 SP142 IHC assay). Although efficacy correlated with PD-L1 expression on tumor cells (TC) and tumor-infiltrating immune cells (IC), an OS benefit was also observed in pts with PD-L1–negative tumors (i.e., TC0 and IC0; HR, 0.75 [95% CI: 0.59, 0.96]). To determine whether these results were consistent across PD-L1 IHC assays, we assessed atezo efficacy in PD-L1 subgroups as defined by SP142 and Dako 22C3 pharmDx PD-L1 IHC assays.

Methods: PD-L1 expression was assessed prospectively with SP142 and retrospectively with 22C3. The SP142 assay measured PD-L1 expression on TC and IC, while the 22C3 assay gave a tumor proportion score (TPS) based on TC membrane staining.

Results: Among the primary population of 850 pts (ITT850), 400 had results from the 22C3 assay (biomarker-evaluable population [BEP]). Clinical outcomes in the BEP vs ITT850, and prevalence in PD-L1 subgroups are summarized (Table). Among pts with tumors negative by SP142 (TC0 and IC0), most (77%) were also negative by 22C3 (TPS $<$ 1%). Comparable OS benefit with atezo was seen in PD-L1–negative subgroups defined by both assays. Improved clinical benefit was observed in pts with the highest PD-L1 expression by either assay (TC3 or IC3 by SP142, or TPS $\geq$ 50% by 22C3; Table).

Conclusions: Prevalence of PD-L1 subgroups in the BEP was consistent with previous reports for both assays. Most tumors considered negative by SP142 were also negative by 22C3. An OS benefit (atezo vs doc) was observed in PD-L1–negative subgroups defined by either assay and was consistent with the overall population results from OAK. These data provide evidence of atezo OS benefit in pts with PD-L1–negative tumors irrespective of the PD-L1 IHC assay used.

Table: 1296O

Clinical efficacy in OAK ITT850 and BEP populations

	ITT850 (N = 850)	BEP (N = 400)
OS HR (atezo vs doc) (95% CI)	0.73 (0.62, 0.87)	0.56 (0.44, 0.71)
PFS HR (atezo vs doc) (95% CI)	0.95 (0.82, 1.10)	0.75 (0.61, 0.93)
Prevalence of PD-L1 subgroups in OAK BEP (n = 400)		
	SP142	**22C3**
PD-L1 negative TC0 and IC0, or TPS < 1%	38%	55%
PD-L1 positive TC1/2/3 or IC1/2/3, or TPS ≥ 1%	62%	46%
PD-L1 high TC3 or IC3, or TPS ≥ 50%	18%	25%
OS HR (atezo vs doc) in PD-L1 subgroups in OAK BEP (n = 400) (95% CI)		
	SP142	**22C3**
PD-L1 negative TC0 and IC0, or TPS < 1%	0.55 (0.37, 0.80)	0.61 (0.45, 0.84)
PD-L1 positive TC1/2/3 or IC1/2/3, or TPS ≥ 1%	0.58 (0.42, 0.78)	0.51 (0.36, 0.73)
PD-L1 high TC3 or IC3, or TPS ≥ 50%	0.37 (0.20, 0.66)	0.49 (0.29, 0.80)

Clinical trial identification: NCT02008227

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

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1297O Randomized results of fixed-duration (1-yr) vs continuous nivolumab in patients (pts) with advanced non-small cell lung cancer (NSCLC)

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Background: Nivolumab, the anti-programmed death (PD)-1 antibody, has demonstrated durable responses and survival benefit in pts with advanced NSCLC, with some pts continuing to derive benefit even after discontinuation of nivolumab (due to adverse events [AEs] or a stopping rule). This raises the question of whether continuous nivolumab treatment is necessary for long-term benefit. CheckMate 153 (NCT02066636), an ongoing phase IIIB/IV study conducted primarily in the community setting, is evaluating the clinical benefit of a fixed-duration (1 yr) of nivolumab treatment vs continuous treatment in pts with previously treated advanced NSCLC. Pts who remained on nivolumab treatment for 1 yr were randomized to either continue receiving treatment or to stop treatment.

Methods: Pts with stage IIIB/IV NSCLC and ≥1 prior systemic therapy were enrolled and treated with nivolumab 3 mg/kg IV Q2W. The primary objective of the study overall was the incidence of high-grade (grade 3–5) select treatment-related AEs. Pts still on treatment at 1 yr were randomized 1:1 either to continue nivolumab until progressive disease, unacceptable toxicity, or withdrawal of consent (continuous-treatment arm), or to discontinue treatment, with the possibility of resuming treatment upon disease progression (fixed-duration arm). Prespecified exploratory objectives included safety and efficacy in the 2 randomized arms.

Results: As of April 2016, 1375 pts were enrolled and treated; 218 pts were randomized after 1 yr of treatment to the continuous-treatment arm (n = 111) or the fixed-duration arm (n = 107). Of these 218 pts, 133 (61%) had received ≥2 prior therapies and 10 (5%) had baseline ECOG PS 2. Data from an upcoming database lock (at which time, the expected post-randomization follow-up ≥10.7 mo) will be presented for randomized pts and will include overall survival, progression-free survival, and safety. In addition, data from pts who were re-treated in the fixed-duration arm will be presented.

Conclusions: The results from CheckMate 153 represent the first insights from a randomized trial evaluating the impact of stopping treatment with a PD-1/PD-L1 inhibitor at 1 yr vs continuing treatment in pts with advanced, previously treated NSCLC.

Clinical trial identification: NCT02066636

Legal entity responsible for the study: Bristol-Myers Squibb

Funding: Bristol-Myers Squibb

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1300PD Impact of co-occurring genomic alterations on overall survival of BRAF V600E and non-V600E mutated NSCLC patients: Results of the Network Genomic Medicine

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Background: Activating BRAF mutations are found in 1-3% of lung adenocarcinomas. Treatment with a combination of a BRAF- and a MEK-inhibitor is now the approved standard therapy for V600E mutated patients. The molecular co-alterations that drive the heterogeneity of BRAF mutated lung cancer patients (pts) are poorly characterized by the lack of multiplex diagnostics results. Frequently used single gene tests are unable to detect co-occurring mutations and their mutual impact on overall survival. The Network Genomic Medicine (NGM) performs high sensitive next generation

sequencing (NGS) based diagnostics on a central platform in Cologne for inoperable lung cancer pts in Germany.

Methods: The NGS panel used in NGM consists of 17 genes to cover potentially targetable aberrations and is run on Illumina (MySeq) platform. In 2016, we have started the retrospective evaluation of BRAF mutated pts with available clinical data and given consent who had received NGS-based molecular diagnostics. In particular, we have focused on BRAF V600E and non-V600E mutated lung cancer pts with and without co-occurring mutations: their frequency, significance and impact on overall survival.

Results: We have analyzed 174 pts (V600E=55 pts, non-V600E=119 pts) with eligible clinical data. Co-occurring mutations were detected in 121 BRAF mutated pts (70%). The most frequent co-alteration was found in TP53 for 89 pts (74%). Regardless of treatment regime, BRAF mutated lung cancer pts without co-alterations seem to have a better overall survival (OS) with 15 versus 13 month ($p = 0.463$), same data for the TP53 co-mutated pts ($p = 0.449$). Likewise, non-targeted treatment of V600E mutation seems to be a negative prognostic factor with OS = 15 month versus 22 month in non-V600E mutated pts ($p = 0.957$).

Conclusions: We report for the first time to our knowledge the heterogeneity of BRAF mutated lung cancer pts in the largest cohort. This work provides evidence that co-occurring genomic alterations influence the overall survival of these pts and stresses the relevance of the multiplex genotyping. Further data including therapies, co-alterations in V600E and other clinicopathologic parameters will be provided.

Legal entity responsible for the study: University Hospital of Cologne for the Network Genomic Medicine

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1301PD Three-year follow-up from CheckMate 017/057: Nivolumab versus docetaxel in patients with previously treated advanced non-small cell lung cancer (NSCLC)

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Background: Long-term data comparing outcomes with immune checkpoint inhibitors versus chemotherapy in NSCLC are limited. The phase 3 trials CheckMate 017 and 057 demonstrated improved overall survival (OS), objective response rates (ORR), and quality of life, as well as a favorable safety profile, with the anti-programmed death (PD)-1 antibody nivolumab versus docetaxel in patients with previously treated advanced squamous and non-squamous NSCLC, respectively. Updated results based on a minimum follow-up of 3 y are reported.

Methods: Patients were randomized 1:1 to receive nivolumab 3 mg/kg Q2W (with option to change to 480 mg Q4W after Sep 2016) or docetaxel 75 mg/m^2 Q3W until progression or discontinuation. After completion of the primary analyses, patients who ended treatment with docetaxel could cross over to receive nivolumab. The primary endpoint of each study was OS; other endpoints were ORR, progression-free survival, and efficacy by PD ligand 1 (PD-L1) expression.

Results: After a minimum follow-up of 36.6 mo in each study (Feb 2017 database locks), 6% of the 427 total patients randomized to the 2 nivolumab arms remained on treatment; no patients remained on docetaxel. Nivolumab continued to show an OS benefit versus docetaxel, with 3-y OS rates of 16% versus 6% in CheckMate 017 and 18% versus 9% in CheckMate 057. Similar to prior reports, an OS benefit was observed in squamous NSCLC regardless of PD-L1 expression, and in non-squamous NSCLC was enhanced at higher PD-L1 expression levels (Table). Of 427 patients in the combined nivolumab arms, 71 (17%) had OS $\geq$ 3 y. Additional 3-y data across trial endpoints will be presented.

Conclusions: With $\geq$3 y of follow-up from 2 randomized phase 3 studies, nivolumab continued to demonstrate an OS benefit versus docetaxel in patients with advanced squamous and non-squamous NSCLC. Overall, 3-y survival was achieved in 17% of nivolumab-treated patients.

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Legal entity responsible for the study: Bristol-Myers Squibb

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Table: 1301PD

OS[a] overall and by PD-L1 expression level	CheckMate 017 (squamous NSCLC)			CheckMate 057 (non-squamous NSCLC)		
	Nivolumab	Docetaxel	HR (95% CI)	Nivolumab	Docetaxel	HR (95% CI)
Overall, n	135	137	–	292	290	–
3-y OS rate, %	16	6	0.62 (0.48, 0.80)	18	9	0.74 (0.62, 0.89)
PD-L1 <1%, n	54	52	–	108	101	–
3-y OS rate, %	13	4	0.60 (0.40, 0.90)	11	8	0.91 (0.68, 1.21)
PD-L1 $\geq$1%, n	63	56	–	123	123	–
3-y OS rate, %	14	9	0.74 (0.50, 1.09)	26	10	0.58 (0.44, 0.76)
PD-L1 $\geq$50%, n	17	10	–	66	46	–
3-y OS rate, %	29	20	0.68 (0.27, 1.66)	39	9	0.35 (0.22, 0.55)

[a]Kaplan-Meier estimates CI = confidence interval; HR = hazard ratio

1302PD IFCT-1502 CLINIVO: Real-life experience with nivolumab in 600 patients (pts) with advanced non-small cell lung cancer (NSCLC): Efficacy and safety of nivolumab and post-nivolumab treatment in the French Expanded Access Program (EAP)

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Background: Nivolumab is a standard option for second-line treatment in pts with advanced NSCLC. Real-life data are lacking regarding the efficacy of nivolumab and post-nivolumab treatment.

Methods: This analysis included the first 600 consecutive pts with stage IIIB/IV NSCLC who received ≥1 dose of nivolumab 3mg/kg q2w through the French EAP from 01/2015 for Squamous (Sq) and 06/2015 for Non-Sq NSCLC, until 08/2015.

Results: Median age was 64 yo, there were 409 (68%) men, 521 (87%) smokers, 478 (80%) PS0/1 pts, 230 (38%) Sq and 370 (62%) Non-Sq NSCLC, 130 (22%) pts with brain metastases. Nivolumab was administered as $2^{nd}/3^{rd}/\geq 4^{th}$-line for 26%/33%/41% pts, respectively. Best response was PR/SD/PD for 17%/30%/37% of patients, respectively, with 16% not assessable. Toxicities occurred in 187 (31%) pts, including 10% grade ≥3 events. After a median follow-up of 22.1 (95% CI 21.6-22.6) months, median PFS and OS from the initiation of nivolumab were 2.1 (95%CI 1.9-2.3) and 9.5 (95%CI 8.4-10.8) months, respectively. Post-nivolumab treatment was administered to 262 (44%) pts, and mostly consisted of gemcitabine (19%), docetaxel (18%), paclitaxel (14%), erlotinib (12%), vinorelbine (9%), platin-based doublet (8%), or pemetrexed (8%). Access to post-nivolumab treatment was higher in PS0/1 vs. PS2 pts (48% vs. 23%, $p < 0.001$), but was not different according to histology or treatment line or disease control with nivolumab. Best response to post-nivolumab treatment was PR/SD/PD for 15%/42%/42% of pts, respectively. In the whole cohort, median post-nivolumab OS was 4.0 (95%CI 2.8-4.6) months, and was significantly higher in case of PR to nivolumab (HR = 0.38; 95%CI 0.23-0.64; $p < 0.001$), and if subsequent treatment was delivered (HR = 0.30; 95%CI 0.24-2.13; $p = 0.001$); median post-nivolumab OS in pts receiving post-nivolumab treatment was 7.5 (95%CI 6.8-8.7) months, and did not differ based on histology or treatment line.

Conclusions: Efficacy and safety of nivolumab was in line with available data. Post-nivolumab treatment may be delivered in many pts, and impact OS. Data on the whole cohort of 900 pts enrolled in the EAP will be presented.

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Legal entity responsible for the study: French Cooperative Thoracic Intergroup (IFCT), Paris, France

Funding: BMS

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1303PD Nivolumab in previously treated patients with metastatic squamous NSCLC: Results of a European single-arm, phase 2 trial (CheckMate 171) including patients aged ≥70 years and with poor performance status

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Background: Nivolumab, a fully human PD-1 immune checkpoint inhibitor antibody, demonstrated a favorable efficacy and safety profile in previously treated SQ NSCLC in a phase 3 trial (CheckMate 017), with significantly longer OS (median 9.2 mo) and fewer treatment-related (TR) grade 3–4 AEs (7%) vs. docetaxel (median OS: 6.0 mo; grade 3–4 TRAEs: 55%). In a North American community-based study (CheckMate 153; SQ/non-SQ NSCLC), nivolumab showed comparable efficacy and safety to that observed in controlled clinical trials.

Methods: Patients aged ≥18 yr from 13 European countries with advanced SQ NSCLC, progressive disease after ≥1 systemic treatment, and ECOG performance status (PS) 0–2 were eligible to receive nivolumab. The primary objective of the study (NCT02409368) was to evaluate safety. OS and ORR were secondary objectives.

Results: 809 patients were enrolled: 79% male and 93% current/former smokers. Most patients had received 1 (42%) or 2 (40%) prior lines of therapy. Median duration of nivolumab therapy was 4.4 mo (range: 0.0, >14.7). 324 patients (40%) were continuing treatment at database lock. 403 patients (50%) had TRAEs. 95 (12%) had grade 3–4 TRAEs, most frequently asthenia (12 [2%]) and fatigue (10 [1%]). Of the 5 cases (1%) of TR grade 3–4 pneumonitis, 3 had a documented resolution, and in these patients, resolution occurred within 5 wk. TRAEs led to treatment discontinuation in 45 patients (6%), most commonly pneumonitis, asthenia, and fatigue (7, 5, and 5 patients each). 2 deaths were deemed TR. Median OS was 9.9 mo (95% CI: 8.7, 13.1). In the subgroup aged ≥70 yr (n = 279), 155 patients (56%) had TRAEs and 16 (6%) discontinued due to TRAEs. In the subgroup with ECOG PS 2 (n = 98), 45 patients (46%) had TRAEs and 5 (5%) discontinued due to TRAEs. Additional data including outcomes in the age ≥70 yr and ECOG PS 2 subgroups will be presented.

Conclusions: The safety of nivolumab in this study was consistent with prior studies of nivolumab in previously treated SQ NSCLC, with no new safety signals. Tolerability in patients aged ≥70 yr or with ECOG PS 2 was comparable to the overall population.

Clinical trial identification: NCT02409368

Legal entity responsible for the study: Bristol-Myers Squibb

Funding: Bristol-Myers Squibb and Ono

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1304PD Correlation of radiation pneumonitis history before nivolumab and onset risk of interstitial lung disease or progression free survival of nivolumab in patients with non-small cell lung cancer

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Background: Nivolumab (Nivo) demonstrated the promising efficacy for patients (pts) with non-small cell lung cancer (NSCLC) as second or later line treatment. And, abscopal effect of the immune checkpoint inhibitor after the radiotherapy (RT) attracts attention. However, it has not clarified the correlation of radiation pneumonitis history (RPH) before Nivo and onset risk of interstitial lung disease (ILD) or progression free survival (PFS) of Nivo. So we retrospectively analyzed the correlation of RPH before Nivo and onset risk of ILD or PFS of Nivo treatments in patients with NSCLC.

Methods: 201 pts treated with Nivo from December 2015 to July 2016 were retrospectively reviewed. This study was multicenter study conducted by the three respiratory medical centers in Japan. We collected clinical data including age, sex, smoking history, histological types, performance status (PS), RPH, and history of RT to chest field, at the time of starting Nivo. And we evaluate the ILD and efficacy. We investigated relationship between RPH and ILD or PFS. The data cut off was on the end of November 2016.

Results: Median age was 68 years old, 135 pts were male, 157 pts had smoking history, 153 pts were PS 0 or 1, 34 pts experienced radiation pneumonitis before Nivo, and 50 pts received the RT to chest field (31 pts were curative RT). For all participants, median PFS was 2.8 months (M), overall ILD rate was 12.4%. In the incidence of ILD, no RPH vs RPH; 9.6% vs 26.5% (relative risk ratio (RRR): 2.76, 95% confidence interval (CI): 1.33-5.73), non-RT to chest field vs RT to chest field; 8.6% vs 22.0% (RRR: 2.37, 95% CI: 1.15-4.88). Furthermore, median PFS was no RPH vs RPH; 2.3 M vs 3.6 M, non-RT to chest field vs RT to chest field; 2.2 M vs 3.3 M, and in univariate analysis, RPH had a trend with PFS (hazard ratio (HR): 0.71, 95% CI: 0.44-1.10), however RT to chest field did not correlate with PFS (HR: 1.02, 95% CI: 0.69-1.47). In multivariate analysis, RPH significantly correlated with PFS (HR: 0.58, 95% CI: 0.35-0.93).

Conclusions: The RPH before Nivo not only gives onset risk of ILD but also contributes to the prolongation of PFS of Nivo.

Clinical trial identification: Protoco; number: UMIN000025908 release date: 31th January, 2017

Legal entity responsible for the study: Fumio Imamura

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1305PD Whole body PD-1 and PD-L1 PET in pts with NSCLC

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Background: Tumor PD-L1 IHC relates moderately with treatment outcome following anti-PD1 therapy in pts with NSCLC and single biopsies do not account for tumor heterogeneity. Aim: 1. Assess safety of the PET procedures. 2. Quantify ^{89}Zirconium-labeled nivolumab (^{89}Zr-nivo) and ^{18}F-labeled BMS-986192 (^{18}F-PD-L1) uptake. 3. Assess tracer uptake heterogeneity. 4. Correlate tracer uptake with PD-1/PD-L1 IHC in tumor, stroma and with treatment outcome.

Methods: NSCLC pts eligible for treatment with nivolumab were included. Pts received whole body ^{18}F-PD-L1 and ^{89}Zr-nivo PET scans. Baseline tumor biopsy was required to assess PD-(L)1 IHC status (28.8 assay). SUV_{peak} was calculated for delineable lesions and correlated to PD-(L)1 IHC and response after 12 wks of nivolumab treatment.

Results: 10 pts (3 $\geq$50%, 5 $\geq$1%, 5 negative by PD-L1 IHC) were enrolled and 37 lesions analysed. No toxicity related to radiotracer was observed. Tumor uptake of both tracers was visualized in all pts, but not in all lesions. Tracer uptake varied among pts with mean ^{18}F-PD-L1 SUV_{peak} 4.6, range 0.5 - 14.4 and mean ^{89}Zr-nivo SUV_{peak} 5.0, range 1.6 – 11 ($p = 0.03$) and within pts with mean SUV_{peak} difference 3.6-fold ($\pm$2.1) and 2.4-fold ($\pm$0.77) between lesions for ^{18}F-PD-L1 and ^{89}Zr-nivo, respectively. For lesions with $\geq$50% PD-L1 IHC, mean ^{18}F-PD-L1 SUV_{peak} was 8.0 ($\pm$4.7) as compared to 3.5 ($\pm$1.6) for lesions with <50% PD-L1 IHC ($p = 0.03$). For tumors with high TIL/stromal PD-1 expression, mean ^{89}Zr-nivo SUV_{peak} was 8.6 ($\pm$2.4) as compared to 6.1 ($\pm$2.1) for lesions with low PD-1 expression ($p = 0.1$). Mean SUV_{peak} for ^{18}F-PD-L1 was 8.4 ($\pm$5.4) for pts with PR and 4.5 ($\pm$2.9) for pts with PD/SD ($p = 0.3$). Mean SUV_{peak} for ^{89}Zr-nivo was 7.8 ($\pm$1.8) for pts with PR and 5.4 ($\pm$2.2) for pts with PD/SD ($p = 0.2$).

Conclusions: 1. PET-imaging with both tracers is safe and feasible, with good tumor-to-normal tissue contrast. 2. Tumor uptake showed heterogeneity among pts and among tumors within pts. 3. Pts with $\geq$50% tumor PD-L1 expression showed higher ^{18}F-PD-L1 uptake. 4. Pts with high PD-1 expression showed higher ^{89}Zr-nivo uptake, and pts with PR demonstrated higher ^{18}F-PD-L1 and ^{89}Zr-nivo tracer uptake than pts with PD/SD, although these are without statistical significance which may be due to the small dataset.

Clinical trial identification: EUDRA-CT-number: 2015-004760-11

Legal entity responsible for the study: Joop de Langen

Funding: Bristol-Myers Squibb

Disclosure: E. Smit: Has an advisory role at Lilly. Received research funding from Company: Boehringer Ingelheim, Bayer, Roche/Genentech and AstraZeneca (paid to institution). D.K. Leung, R.A. Smith, L.M. Wilson, W. Hayes: Is employed at BMS and owns stock and/or other ownership interests in BMS. All other authors have declared no conflicts of interest.

1306PD Hyperprogressive disease (HPD) is frequent in non-small cell lung cancer (NSCLC) patients (pts) treated with anti PD1/PD-L1 monoclonal antibodies (IO)

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Background: Using Tumor Growth Rate (TGR), we previously described HPD in 10% of 89 NSCLC pts treated with IO in a single institution. In this retrospective study, we explored HPD in a larger and multicenter cohort of advanced NSCLC pts treated with IO.

Methods: We performed a clinical and radiological retrospective analysis of consecutive NSCLC pts, treated with IO, in 5 different institutions, between November 2012 and March 2017. Eligibility criteria required, for each patient, 3 CT scans performed before IO, at baseline and during IO respectively, centrally reviewed by a senior radiologist and assessed according to RECIST 1.1 criteria. We calculated TGR at baseline of IO (baseline CT scan (n) vs (n-1) CT scan), TGR during IO (n + 1 CT scan vs baseline) and the variation per month of TGR between both (delta TGR). Pts were defined HPD if the absolute delta TGR increased by at least 50%. Median overall survival (mOS) and median progression free survival (mPFS) were estimated using the Kaplan-Meier method and compared between HPD and not HPD using the log-rank test.

Results: 242 pts were eligible. 64% were male, 50% $\geq$65 years, 51% smokers, 10% PS $\geq$ 2, 63% adenocarcinoma. 19% of NSCLC had KRAS mutation, 2% EGFR mutation, 2% ALK rearrangement, 35% had unknown molecular status. PD-L1 expression was positive in 12% of pts, negative in 11% and unknown in 77%, more than 90% of pts received single agent PD1-inhibitor in $\geq$ 2 line. Response rate (RR) to IO, mPFS and mOS were respectively 15%, 3.9 months (m) [3; 5], 13.4m [9; 42], median follow up was 10m [8; 12]. Compared to baseline, TGR decreased during IO (delta TGR $\leq$0) in 64% of pts, increased (delta TGR>0) in 36% (not regressing tumors). 40 pts (16%) had HPD. Only 3 pts (1,2%) had confirmed pseudoprogression, 2 of them were initially

qualified as HPD. Tumor burden baseline, clinical, molecular, pathological characteristics, PD-L1 status and RR to treatment before IO were not different between HPD and not-HPD pts. Compared to not-HPD population, HPD pts had significantly lower mPFS (1.4 vs 4.9m, $p < 0.001$) and mOS (3.4 vs 17m, $p < 0.001$).

Conclusions: HPD occurs in 16% of 242 advanced NSCLC pts treated with IO, leading to decreased survival. Further work is needed to better characterize this population.

Legal entity responsible for the study: Benjamin Besse

Funding: Gustave Roussy

Disclosure: C. Audigier Valette: Bristol Myers Squibb V. Westeel: BMS, MSD, Merck, AZ B. Duchemann: Bristol-Myers Squibb, Roche D. Planchard: AstraZeneca Boehringer Ingelheim BMS Lilly MSD Pfizer Roche Novartis Chugai J-C. Soria: AstraZeneca, Astex, Clovis, GSK, Gammamabs, Lilly, MSD, Mission Therapeutics, Merus, Pfizer, Pharmamar Pierre Fabre, Roche-Genentech, Sanofi, Servier, Symphogen, Takeda. All other authors have declared no conflicts of interest.

1307PD Detection of driver and resistance mutations in leptomeningeal metastases of NSCLC by next-generation sequencing of cerebrospinal fluid circulating tumor cells

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Background: Leptomeningeal metastases (LM) are more common in non-small cell lung cancer (NSCLC) with *EGFR* mutations. The diagnosis is difficult by traditional imaging only, and leads to poor understanding of resistance mechanisms of LM.

Methods: We compared the CellSearch Assay™, the Thinprep cytologic test (TCT), and brain magnetic resonance imaging (MRI) in 21 NSCLC patients with suspected LM. Next-Generation sequencing that included 416 cancer-associated genes was also performed on cerebrospinal fluid circulating tumor cells (CSFCTCs) of 19 patients.

Results: Twenty-one patients were diagnosed with LM, and CSFCTCs were captured by CellSearch in 20 patients (median, 969 CSFCTCs/7.5 mL; range, 27–14,888). CellSearch had a sensitivity of 95.2% for LM diagnosis, which was higher than that of TCT (12/21, 57.1%), MRI (10/21, 47.6%), and MRI plus TCT (19/21, 90.5%), respectively. CTCs were found only in 5 of 14 patients (median, 2 CTCs/7.5 mL; range, 2–4), which was a much lower ratio than CSFCTCs. Genetic profiles of CSFCTCs were highly concordant with molecular mutations identified in the primary tumor (17/19, 89.5%). The resistance gene *EGFR* T790M was detected in 7 of 9 patients with extracranial lesions, but was only detected in 1 of 14 CSFCTCs samples. Other potential resistant mutations such as *MET* amplification and *ERBB2* mutation were also identified in CSFCTCs.

Conclusions: CellSearch could be a more sensitive method for detecting tumor cells in CSF, and potentially provides earlier diagnosis of LM. More importantly, CSFCTCs could be an important and new way of "liquid biopsy" for genetic profiles of metastatic tumor cells in LM patients of NSCLC.

Legal entity responsible for the study: Yi-Long Wu

Funding: Geneseeq Biotechnology, Inc., Nanjing, China

Disclosure: All authors have declared no conflicts of interest.

1308PD Preliminary efficacy and safety of lorlatinib in patients (Pts) with ROS1-positive non-small cell lung cancer (NSCLC)

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Background: Most pts with ROS1-rearranged NSCLC achieve initial benefit with crizotinib but subsequently develop resistance, and further treatment options are limited. In Phase 1 of this study, lorlatinib, a potent and brain-penetrant TKI, was associated with a response rate of 50% in ROS1-positive NSCLC pts, most of whom had central nervous system (CNS) metastases (mets) and a majority of whom had received prior crizotinib. Antitumor activity and safety were explored at the recommended Phase 2 dose.

Methods: In this ongoing, Phase 2 study (NCT01970865), pts with ROS1+ NSCLC, ± asymptomatic untreated or treated CNS mets were enrolled with no restriction on the type or number of prior lines of therapy. Pts received lorlatinib 100 mg QD. The primary objective was overall and intracranial (IC) antitumor activity, measured as overall and IC response by independent central review.

Results: 23 pts with ROS1+ NSCLC were treated; 12 had CNS involvement, 16 had received prior crizotinib and 1 had received prior crizotinib and ceritinib. The overall response rate (ORR) by investigator assessment for this cohort was 8/23 (34.8%; 95%

Table: 1307PD

Patient No.	Primary gene profile	Targeted therapy before LM	Rebiopsy gene profile	CSFCTCs gene profile (NGS)
1	*EGFR* L858R (lung)	Erlotinib	*EGFR* L858R (lung, ARMS); MET(IHC):80% (3+)	*EGFR* L858R
2[b]	*EGFR* del19 (lymph node)	Icotinib	UA	*EGFR* del19; *EGFR* T790M
3	EML4-ALK (lung)	Crizotinib	EML4-ALK (pleural effusion)	EML4-ALK; MET amplification
4	*EGFR* 20INS (lung)	None	UA	*EGFR* 20INS
5	*EGFR* del19 (pleura)	Gefitinib	*EGFR* del19 and T790M (lung)	*EGFR* del19; *EGFR* amplification
6	*EGFR* L858R (lung)	Erlotinib	*EGFR* L858R and T790M (lung)	*EGFR* L858R
7	*EGFR*, ALK (WT)	None	Snapshot, MET, KIT (WT)	Common driver gene (WT)
9	*EGFR* del19 (pleura)	Gefitinib	*EGFR* del19 and T790M (liver);MET: 100% (3+) (liver)	*EGFR* del19; *ERBB2* exon8 T328fs; *ROS1* exon7 W215X
10	*EGFR* L858R (lung)	Gefitini, erlotinib	*EGFR* del19 and T790M (lung)	*EGFR* del19
11	*EGFR* L858R (lung)	Gefitini, erlotinib	UA	*EGFR* L858R
12	*EGFR* L858R (lung)	Gefitinib	*EGFR* L858R and T790M (plasma)	Common driver gene (WT)
13	EML4-ALK (lung)	Crizotinib	UA	EML4-ALK
14	*EGFR* del19 (lung)	Erlotinib, afatinib	UA	*EGFR* del19; MET amplification
15	*EGFR* del19 (lung)	Icotinib	UA	*EGFR* del19
16	*EGFR* L858R (lung)	None	*EGFR* L858R (lymph node)	*EGFR* and ALK (WT); *RET* exon4 V253E
17	*EGFR* L861Q (lymph node)	Erlotinib	UA	*EGFR* L861Q; *EGFR* del19
18[c]	*EGFR* L858R (lung)	Gefitinib	*EGFR* L858R and T790M (lung)	*EGFR* L858R; *PIK3CA* exon2 N107S; *MET* exon11 F839L
19	*EGFR* L858R (lung)	Gefitinib	*EGFR* L858R and T790M (lung)	*EGFR* L858R
21	*EGFR* L858R (lung)	Gefitinib	UA	*EGFR* L858R

CI: 16.4, 57.3). The best overall response was SD in 11 pts (47.8%) and progressive disease (PD) in 2 pts (8.7%). The disease control rate at 12 weeks was 17/23 (73.9%; 95% CI: 51.6, 89.8). Of 8 pts with a confirmed response, 3 have progressed (after a range of 3.5–7.0 mos) and the remainder are in follow-up (range: 5.6–8.3 mos). The IC-ORR was 3/12 (25%) (95% CI: 5.5, 57.2). The most commonly reported treatment-related adverse events (TRAEs) were hypercholesterolemia (95.7%) and hypertriglyceridemia (69.6%) both managed with statins or other lipid lowering agents. Additional TRAEs included peripheral edema (34.8%) and cognitive effects (30.4%). Treatment-related dose interruptions and dose reductions occurred in 26.1% and 17.4% of pts, respectively; there were no treatment-related discontinuations or deaths. Most pts remain on treatment.

Conclusions: Lorlatinib has shown clinical activity in ROS1+ NSCLC pts, a majority of whom had CNS involvement and most of whom had received prior crizotinib. Overall, lorlatinib was well-tolerated with lipid elevations being the most common TRAEs.

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1309P Efficacy and safety of necitumumab and pembrolizumab combination therapy in patients with stage IV non-small cell lung cancer (NSCLC)

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Background: Studies of EGFR-directed monoclonal antibody (mAb) necitumumab (neci) and anti-PD1 pembrolizumab (pembro) demonstrate activity of each agent in NSCLC.

Methods: This phase 1b, multicenter, single arm study of neci and pembro examined the safety, efficacy, and tolerability in pretreated patients with Stage IV NSCLC (NCT02451930). PDL1 was centrally assessed retrospectively using IHC 22C3 pharmDx assay (negative, weak positive, strong positive if $< 1\%$, 1-49%, $\geq 50\%$ of tumor cells were stained, respectively). Escalating doses of neci 600 – 800 mg IV (days 1 and 8 every 3 weeks [Q3W]) were administered with pembro (200 mg IV) on Day 1 Q3W (Part A). Established dose from Part A was used in the expansion cohort (Part B). Study objectives were to determine the dose-limiting toxicity (DLT) and evaluate tolerability and overall response rate (ORR) by RECIST 1.1. Secondary objectives included progression-free survival (PFS) and overall survival (OS).

Results: for 64 patients are reported. Part A completed without DLTs (9 patients; 2 squamous, 7 nonsquamous). Overall, 3 patients received neci 600 mg and 61 patients received neci 800 mg; all patients received pembro 200 mg. ORR (95% CI) was 23.4% (13.8, 35.7). Median PFS (95% CI) was 4.1 m (2.4, 6.9). Six-month OS rate (95% CI) was 74.7% (61.5, 83.9). Treatment-emergent adverse events occurring in $\geq 20\%$ of all patients (n (%)) included dermatitis acneiform: 43 (67.2); asthenia: 24 (37.5); dry skin: 23 (35.9); hypomagnesemia: 21 (32.8); fatigue: 20 (31.3); decreased appetite and diarrhea (each): 17 (26.6); headache, pruritus, and stomatitis (each): 14 (21.9). Two neci 800 mg + pembro patients experienced grade 5 respiratory tract infection.

Conclusions: The results suggest modest activity of the combination in a NSCLC patient population with a relatively high proportion of PDL1 negative tumors (Table).

Table: 1309P

	Necitumumab 600 mg/800 mg + Pembrolizumab 200 mg		
	Overall (N = 64)	**Squamous (n = 30)**	**Nonsquamous (n = 34)**
Age, median (range), y	65 (43, 81)	67.5 (48, 81)	61 (43, 75)
Male, n (%)	46 (71.9)	23 (76.7)	23 (67.6)
Prior systemic therapy, n (%)			
1 line	36 (56.3)	22 (73.3)	14 (41.2)
2 lines	15 (23.4)	5 (16.7)	10 (29.4)
≥3 lines	13 (20.3)	3 (10.0)	10 (29.4)
Baseline ECOG PS, n (%)	64 (100)	30 (100)	34 (100)
0	17 (26.6)	3 (10.0)	14 (41.2)
1	46 (71.9)	26 (86.7)	20 (58.8)
2	1 (1.6)	1 (3.3)	0
Tobacco use, n (%)	64 (100)	30 (100)	34 (100)
Former	41 (64.1)	21 (70.0)	20 (58.8)
Current	14 (21.9)	7 (23.3)	7 (20.6)
Never	9 (14.1)	2 (6.7)	7 (20.6)
Ef˚cacy			
ORR n (%) (95% CI)	15 (23.4) (13.8, 35.7)	6 (20.0) (7.7, 38.6)	9 (26.5) (12.9, 44.4)
mPFS (months) (95% CI)	4.1 (2.4, 6.9)	2.8 (1.4, 5.5)	6.9 (2.7, 12.3)
6-month OS rate (%) (95% CI)	74.7 (61.5, 83.9)	63.6 (42.8, 78.6)	84.2 (66.0, 93.1)
PDL1 Status	64 (100)	30 (100)	34 (100)
PDL1 negative	32 (50.0)	13 (43.3)	19 (55.9)
ORR n (%) (95% CI)	4 (12.5) (3.5, 29.0)	1 (7.7) (0.2, 36.0)	3 (15.8) (3.4, 39.6)
mPFS (m) (95% CI)	2.69 (1.4, 4.1)		
6-month OS rate (%) (95% CI)	68.2 (47.7, 82.0)		
PDL1 Weak positive	12 (18.8)	7 (23.3)	5 (14.7)
ORR n (%) (95% CI)	3 (25.0) (5.5, 57.2)	1 (14.3) (0.4, 57.9)	2 (40.0) (5.3, 85.3)
mPFS (m) (95% CI)	5.4 (0.8, –)		
6-month OS rate (%) (95% CI)	83.3 (48.2, 95.6)		
PDL1 Strong positive	10 (15.6)	5 (16.7)	5 (14.7)
ORR n (%) (95% CI)	4 (40.0) (12.2, 73.8)	2 (40.0) (5.3, 85.3)	2 (40.0) (5.3, 85.3)
mPFS (m) (95% CI)	7.6 (1.0, 12.3)		
6-month OS rate (%) (95% CI)	80.0 (40.9, 94.6)		
Unknown	10 (15.6)	5 (16.7)	5 (14.7)
ORR n (%) (95% CI)	4 (40.0) (12.2, 73.8)	2 (40.0) (5.3, 85.3)	2 (40.0) (5.3, 85.3)
mPFS (m) (95% CI)	– (0.82, –)		
6-month OS rate (%) (95% CI)	78.8 (38.1, 94.3)		

ECOG PS, Eastern Cooperative Oncology Group performance status; PDL1, programmed death ligand 1; ORR, overall response rate; mPFS, median progression-free survival; OS, overall survival; CI, confidence interval.

Clinical trial identification: NCT02451930

Legal entity responsible for the study: Eli Lilly and Company

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1310P Survival and safety of atezolizumab by best overall response (BOR) in the phase III NSCLC OAK study

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Background: Atezolizumab (atezo; anti–PD-L1) inhibits binding of PD-L1 to PD-1 and B7.1, thereby restoring tumor-specific T-cell immunity. OAK, the first randomized Ph III study of atezo vs docetaxel (doc) in 2L/3L NSCLC demonstrated a superior OS benefit of atezo (HR 0.73; 95% CI: 0.62, 0.87; $P = 0.0003$) in patients (pts) regardless of PD-L1 expression levels on tumor cells (TC) or tumor-infiltrating immune cells (IC). Here we present efficacy and safety analyses in the OAK primary population (n = 850) by BOR subgroups.

Methods: Previously treated pts were randomized 1:1 to atezo (1200 mg) or doc (75 mg/m^2) IV q3w. Co-primary endpoints were OS in ITT and PD-L1 expression subgroup (≥ 1% PD-L1 on TC or IC). Secondary endpoints included ORR and safety. BOR subgroups were defined based on RECIST v1.1 response determined by investigators. Time to response (TTR) was based on tumor assessment every 6 weeks. Data cut-off, July 7, 2016.

Results: Baseline demographics were generally similar across BOR subgroups except for PD-L1 expression status. TC1/2/3 or IC1/2/3 prevalence was 74% in CR/PR, 53% in SD and 55% in PD subgroups, respectively. The survival benefit of atezo vs doc was observed across BOR subgroups with greatest benefit occurring in the CR/PR subgroup (HR, 0.32; 95% CI 0.16, 0.63; see Table). Among pts in the CR/PR subgroup, the median TTR was comparable between atezo and doc arms (2.8 mo each). The median duration of response was longer in the atezo arm pts (16.3 mo, 95% CI: 10.0, NE) vs doc arm pts (6.2 mo, 95% CI: 4.9, 7.6). OS benefit with atezo was also observed in patients with SD and PD as BOR (see Table). No new safety findings were observed among BOR subgroups.

Conclusions: Atezo responses were durable. Atezo responders had more than two-thirds reduction in the risk of death compared with doc responders. In addition, the improved OS with atezo vs doc seen in pts with SD and PD suggests that clinical benefit also extended to patients who did not have a radiographic response.

Table: 1310P Efficacy of atezolizumab vs docetaxel by BOR subgroups

Patient Population	Atezolizumab		Docetaxel		HR (95% CI)[a]
	n	mOS (95% CI), mo	n	mOS, (95% CI) mo	
ITT (N = 850)	425	13.8 (11.8, 15.7)	425	9.6 (8.6, 11.2)	0.73 (0.62, 0.87)
BOR subgroups					
CR/PR	58	NE (NE, NE)	57	20.0 (15.9, NE)	0.32 (0.16, 0.63)
SD	150	17.6 (15.7, 20.2)	177	13.0 (11.5, 14.7)	0.70 (0.53, 0.92)
PD	187	7.3 (6.7, 9.4)	117	6.4 (5.6, 7.3)	0.72 (0.56, 0.93)

[a]Stratified HR for ITT and unstratified HR for subgroups. 95% CI for HR were estimated using Cox regression.
NE, not estimable.

Clinical trial identification: NCT02008227

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

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1311P LKB1 loss is a novel genomic predictor of de novo resistance to PD-1/PD-L1 axis blockade in KRAS-mutant lung adenocarcinoma

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Background: We previously reported that *KRAS*-mutant lung adenocarcinomas (LUAC) with co-occurring genetic events in *STK11/LKB1* (KL) or *TP53* (KP) define subgroups with marked differences in immune contexture, including paucity of infiltrating CD8+ lymphocytes in KL LUACs. Here, we present updated data on the clinical efficacy of PD-1/PD-L1 inhibitors in co-mutation defined *KRAS*-mutant LUAC subsets using data assembled by members of the SU2C/ACS Lung Cancer Dream Team.

Methods: Patients (pts) with metastatic *KRAS*-mutant LUAC who received at least one cycle of PD-1/PD-L1 inhibitor therapy, were alive for ≥14 days thereafter, and had available molecular profiling were identified retrospectively. Efficacy assessment was based on RECIST v1.1. PD-L1 expression was tested using 22C3 pharmDx or E1L3N IHC assays. Isogenic derivatives of the LKR10 *Kras*$^{LA1/+}$ murine LUAC cell line with CRISPR/Cas9-mediated *Lkb1* knockout were used in preclinical experiments.

Results: 192 immunotherapy-treated (82% nivolumab, 12% pembrolizumab, 5% anti-PD1/PD-L1 plus anti-CTLA-4) pts with *KRAS*-mutant LUAC were included in the analysis. The ORR differed significantly between the KL (8.9%), KP (37.9%) and K-only sub-groups (25.8%) ($P = 0.00069$, Fisher's exact test) and was concordant for each genotype across patient cohorts [ORR for KL: 8.3% in the MDA cohort, 8.7% in the MSKCC cohort and 9.5% in the DFCI/MGH cohort). KL LUAC exhibited significantly shorter PFS (mPFS 1.8m vs 3m, HR = 0.47, 95% CI 0.32-0.7, $P = 0.0002$, log-rank test) and OS (mOS 6.8m vs 16.1m, HR 0.48, 95% CI 0.3 to 0.76, $P = 0.0018$, log rank test) compared to *KRAS*-mutant LUAC with wild-type *LKB1*. 11/14 KL tumors with available IHC data were negative for PD-L1 expression. Among 7 PD-L1-negative KP tumors, 3 PRs and 2SDs were recorded. In syngeneic murine models loss of Lkb1 promoted resistance to PD-1 inhibitor monotherapy, suggesting a causative role.

Conclusions: Inactivation of LKB1 represents a novel genomic predictor of *de novo* resistance to PD-1/PD-L1 blockade in *KRAS*-mutant LUAC. In addition to tumor PD-L1 status and tumor mutational burden precision immunotherapy approaches should take into consideration the *LKB1* status of individual tumors.

Legal entity responsible for the study: SU2C/ACS Lung Cancer Dream Team

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Disclosure: M.D. Hellman: Consultant/Advisory Board: Genentech, BMS, Merck, AstraZeneca, Janssen, Novartis Research support- Genentech, BMS. J.V. Heymach: Scientific Advisory Board: Genentech, BMS, AstraZeneca, Eli Lilly, EMD Serono, Boehringer Ingelheim. All other authors have declared no conflicts of interest.

1312P Prediction of survival with durvalumab in locally advanced or metastatic NSCLC using early tumor assessments

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Background: The analysis objective was to assess if limited tumor assessments can predict long-term overall survival (OS) in patients (pts) with locally advanced or metastatic (Stage IIIB-IV) non-small cell lung cancer (NSCLC) treated with durvalumab.

Methods: We used data from a Phase II, non-comparative, open-label multicenter study of durvalumab in NSCLC pts with ≥2 prior systemic treatment regimens,

Table: 1312P

	ATLANTIC (model building)		Study 1108 (validation)	
	Bad Group (n = 157)	**Good Group (n = 34)**	**Bad Group (n = 117)**	**Good Group (n = 58)**
Median OS (95% CI), days	340 (292, 403)	NE (557, NE)	265 (194, 315)	739 (616, NE)
6-month OS rate (95% CI)	0.742 (0.665, 0.804)	0.941 (0.785, 0.985)	0.605 (0.517, 0.682)	0.937 (0.855, 0.973)
1-year OS rate (95% CI)	0.478 (0.397, 0.554)	0.882 (0.716, 0.954)	0.371 (0.282, 0.460)	0.819 (0.708, 0.891)
HR [Good vs. Bad] (95% CI)	0.2059 (0.0569, 0.4437)		0.2637 (0.1661, 0.4187)	

NE, not estimable

including 1 platinum-based (ATLANTIC). Per exploratory analysis, the first 2 post-baseline assessments were used to develop the model. Using an elastic net statistical method, combined with cross validation, we identified important baseline variables, built a scoring system (defined as 0.28*sex + 0.188*histology group + 0.034*smoker group – 0.176*line of therapy – 0.041*tumor assessment) in which assessments are represented as a single variable (interpreted as a weighted average), and identified the optimal score thresholds to segment pts into 2 groups ('good' vs. 'bad') with significant differences in long-term OS.

Results: As of June 3, 2016, 444 pts had received treatment; 191 from cohort 2 (EGFR/ALK wild-type pts) with sufficient assessments (baseline and ≥1 follow-up) were used to develop the model. Median age was 64.0 years, 61.8% had WHO PS 1, 18.8% had squamous histology, mean number of prior anticancer regimens was 4.0, and 83.7% were current/ex-smokers; PD-L1 expression was high (≥25% of tumor cells stained) in 57.1%, low/negative in 35.6%, and unknown in 7.3%. OS results are summarized in the table. The model was validated using data from a Phase I/II open-label trial of durvalumab (1108).

Conclusions: We developed an algorithm based on baseline characteristics and tumor assessments to segment NSCLC pts treated with durvalumab into 2 groups with distinct OS. The scoring system was independently validated. However, the predictive versus prognostic value of this algorithm needs further evaluation using data from randomized trials.

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Legal entity responsible for the study: AstraZeneca PLC

Funding: AstraZeneca

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1313P Immune-related adverse events (irAEs) in advanced NSCLC patients treated with atezolizumab: Safety population analyses from the Ph III study OAK

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Background: A superior survival benefit with atezolizumab (atezo; anti–PD-L1) vs docetaxel (doc; HR 0.73; 95% CI: 0.62, 0.87) has been demonstrated in OAK, the first randomized Ph III study of atezo in NSCLC patients (pts) who had failed prior platinum therapy. In the primary efficacy population (n = 850), atezo benefit was seen regardless of PD-L1 expression levels on tumor cells (TC) or tumor-infiltrating immune cells (IC). Here, we present the analyses of irAEs in the safety population (N = 1225) of OAK.

Methods: Pts were randomized 1:1 to atezo (1200 mg) or doc (75 mg/m^2) IV q3w. Co-primary endpoints were OS in ITT and in PD-L1 expression subgroups. Secondary endpoints included ORR and safety. irAEs were defined using MedDRA Preferred Terms that included both diagnosed immune conditions and signs and symptoms potentially representative of immune related events, regardless of investigator-assessed causality. Safety analyses conducted were incidence, nature and severity of irAEs, corticosteroid use and irAEs leading to atezo interruption/discontinuation. Data cutoff: July 7, 2016.

Results: In the atezo arm, 6.2% of pts had grade 3-4 irAEs and 25.0% of pts had grade 1-2 irAEs. No grade 5 irAEs were reported. Low rates of any-grade hypothyroidism (3.9%), pneumonitis (1.5%), hepatitis, (1.1%), and colitis (0.3%) were observed. Grade 3-4 irAEs included pneumonitis (0.7%) and hepatitis (0.7%); no pts developed Grade 3-4 colitis. 36 (5.9%) atezo arm pts experienced irAEs requiring corticosteroid treatment. Majority of irAEs in the atezo arm were manageable; 13 pts (2.1%) discontinued atezo. Meningoencephalitis (0.7%) and AST/ALT elevation (0.3%/0.2%) were the most frequently reported irAEs leading to atezo discontinuation. 26 pts (4.3%) had dose interruptions due to irAEs. AST/ALT elevation (0.8%/0.8%) and diarrhea (0.8%) were the most frequently reported irAEs leading to dose interruption.

Conclusions: The irAEs occurring in atezo-treated pts were mostly low grade and manageable, with few pts requiring dose interruption/discontinuation of atezo and corticosteroid treatment. Efficacy data based on irAE subgroups of OAK are presented separately.

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

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1314P Association between immune-related adverse events (irAEs) and atezolizumab efficacy in advanced NSCLC: analyses from the phase III study OAK

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Background: OAK, the first randomized Ph III study of atezolizumab (atezo; anti–PD-L1), demonstrated a superior survival benefit with atezo vs docetaxel (doc) in NSCLC patients (pts) who had failed prior platinum therapy (HR 0.73; 95% CI: 0.62, 0.87). This analysis evaluates the benefit of atezo in pts with and without irAEs from the primary efficacy population (n = 850) of OAK. Safety data are reported separately.

Methods: Pts were randomized 1:1 to atezo (1200 mg) or doc (75 mg/m^2) IV q3w. irAEs were defined using MedDRA Preferred Terms that included both diagnosed immune conditions and signs and symptoms potentially representative of immune related events, regardless of investigator-assessed causality. For this analysis, efficacy was evaluated in pts with and without irAEs in the atezo and doc arms; efficacy endpoints were OS, PFS and ORR. To overcome the inherent survivor bias between irAE subgroups (pts surviving longer may be more likely to have irAEs), OS was evaluated using a time-dependent (TD) Cox model. Additional exploratory analyses included atezo efficacy in pts who did vs did not receive systemic steroids for irAEs. Data cutoff: July 7, 2016.

Results: The incidence of irAEs in the atezo arm was 31% (25.0% grade 1-2, 6.2% grade 3-4, no grade 5). Baseline characteristics including PD-L1 expression on tumor cells or tumor-infiltrating immune cells were generally similar between irAE subgroups. OS per TD Cox model was in favor of atezo arm pts with irAEs vs those without irAEs (HR 0.79; 95% CI: 0.60, 1.05). Median time to onset of first irAE was 1.6 mo; post irAE mOS was 17.3 mo (95% CI: 11.7, 21.2). 24 atezo arm pts (6%) required corticosteroid treatment. Median OS in pts who did vs did not receive corticosteroids was 16.0 mo (95% CI: 10.3, 23.5; n = 24) vs 21.9 mo (95% CI: 16.6, NE; n = 106), respectively. Median PFS was 5.9 mo (95% CI: 2.6, 14.5) vs 5.4 mo (95% CI: 4.2, 8.8) and ORR was 29% (95% CI: 13, 51) vs 21% (95% CI: 13, 30) in pts who did vs did not receive corticosteroids.

Conclusions: In this analysis, irAEs did not negatively impact the survival benefit of atezo. Further investigation on the impact of corticosteroids on atezo efficacy in randomized trials is needed.

Clinical trial identification: NCT02008227

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

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1315P Efficacy and safety data from patients with advanced non-squamous NSCLC and brain metastases from the nivolumab expanded access programme (EAP) in Italy

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Background: Brain metastases are a very common secondary localization of disease in patients (pts) with lung cancer. The prognosis of these pts is still poor and they are usually excluded from clinical trials. The EAP offered an opportunity to evaluate nivolumab treatment in these patients outside of a controlled clinical trial in Italy.

Methods: Nivolumab was available upon physician request for pts aged ≥18 years with a diagnosis of non-squamous non-small cell lung cancer (non-Sq-NSCLC) who had relapsed after a minimum of one prior systemic treatment for stage IIIB/stage IV non-Sq-NSCLC. Nivolumab 3 mg/kg was administered intravenously every 2 weeks to a maximum of 24 months. Pts included in the analysis had received ≥ 1 dose of nivolumab and were monitored for adverse events using Common Terminology Criteria for Adverse Events. Pts with brain metastasis were eligible if asymptomatic, neurologically stable and either off corticosteroids or on a stable dose or decreasing dose of ≤ 10 mg daily prednisone.

Results: Of 1588 patients with non-Sq-NSCLC participating in the EAP in Italy, 409 (26%) had asymptomatic and controlled brain metastases. With a median number of 7 doses (1-45) and a median follow-up of 6.1 months (0.1-21.9), the disease control rate was 40%, including 3 pts with a complete response, 65 patients with a partial response and 96 with stable disease. As of March 2017, median overall survival among patients with brain metastases was 8.1 (6.2-10.1) months. Among these pts, 117 were receiving steroid therapy at baseline and 74 received concomitant radiotherapy. Overall, safety profile and discontinuations for drug-related toxicity were consistent with what observed in the general population.

Conclusions: These preliminary data showed efficacy of nivolumab in patients with non-Sq-NSCLC with brain metastases, with safety results consistent to what already reported in controlled clinical trials, thus supporting the use of nivolumab in this population with poor prognosis.

Clinical trial identification: CA209966

Legal entity responsible for the study: Lucio Crinò

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1316P Efficacy and immune activation with PEGylated human IL-10 (AM0010) in combination with an anti-PD1 in advanced NSCLC: Update

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Background: At therapeutic concentrations, AM0010 stimulates the cytotoxicity, survival and proliferation of intratumoral antigen activated CD8+ T cells in pre-clinical cancer models and in patients. AM0010 activates antigen stimulated CD8 T cells while

PD-1 inhibits them, providing a rationale for combining AM0010 with PD-1 inhibitors.

Methods: 34 NSCLC pts. received AM0010 (10-20mg/kg QD, SC) with pembrolizumab (2mg/kg, q3wk IV; n = 5) or nivolumab (3mg/kg, q2wk IV; n = 29). Tumor responses were assessed by irRC. Immune responses were measured by analysis of serum cytokines (Luminex), activation of blood derived T cells (FACS) and peripheral T cell clonality (TCR sequencing).

Results: Pts had a median of 2 prior therapies. Median follow-up is 12.9 mo (range 3.7-26.9). AMO010 plus anti-PD-1 was well tolerated. All TrAEs were reversible. G3/4 TrAEs included thrombocytopenia (8), anemia (7), fatigue (6), rash (4), pyrexia (2), hypertriglyceridemia (3) and pneumonitis (1). As of May 5 2017, 26 pts had at least 1 tumor assessment, and partial responses (PRs) were observed in 10 pts (38.5%). 12 patients had stable disease (SD: 46.1%). mPFS and mOS were not reached. Updated efficacy data will be available by Aug. 31 2017.

Table: 1316P Preliminary response data stratified for PD-L1 (Study in progress)

NSCLC (n = 26)	PD-L1 (22C3 IHC) (n = 20)			IHC not available n = 6
	<1% (n = 11)	1-49% (n = 4)	≥50% (n = 5)	
PR, n (%)	3 (27%)	2 (50%)	4 (80%)	1 (17%)
SD, n (%)	7 (64%)	(25%)	1 (20%)	3 (50%)

AM0010 plus anti-PD1 increased Th1 and Th2 cytokines and FasL in the serum and led to a sustained increase in the number and proliferation of PD1+ Lag3+ activated CD8+ T cells, suggesting the invigoration of previously exhausted CD8+ T cells. In addition, previously undetectable T cell clones in the blood expanded to rank amongst the most abundant clones in the patient. The magnitude of novel T cell expansion and the number of invigorated CD8+ T cell correlated with objective tumor responses.

Conclusions: AM0010 in combination with anti-PD-1 is well-tolerated in advanced NSCLC pts. AM0010 improved on the expected response rates of nivolumab regardless of PD-L1 status. The observed CD8 T cell activation is promising and encourages the continued study of AM0010 in combination with an anti-PD-1.

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Legal entity responsible for the study: ARMO BioSciences, Redwood City, CA, USA

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1317P Multicenter observational study of the efficacy and safety of nivolumab (Nivo) as 2+ line treatment and quality of life (QoL) in advanced refractory non-small cell lung cancer (NSCLC) patients: Interim analysis

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Background: We aimed to evaluate clinical and patient-reported outcomes of Nivo as ≥ 2nd line treatment in NSCLC pts within the expanded access program. The interim data on response rates, survival and safety as well as base-line QoL and its changes are presented.

Methods: Adult pts with advanced refractory NSCLC received Nivo 3 mg/kg q2w. Tumor response was assessed using RECIST v. 1.1, adverse events (AEs) with NCI CTCAE v3.0; for QoL and symptom assessment RAND SF-36 and ESAS-R were used. Progression-free survival (PFS) and overall survival (OS) from the start of Nivo treatment were evaluated using Kaplan-Meier method. Group QoL comparisons were made using Mann-Whitney and Wilcoxon tests.

Results: At the cut-off 172 pts were enrolled in 7 centers in RF with median follow-up – 19 weeks (mean age – 60 (29 – 80); males – 65%; ECOG PS 0-1/2-3 – 81%/19%; former/current smokers – 71%; non-squamous NSCLC – 65%; ≥2 lines of previous systemic treatment – 51%). At baseline pts had dramatically compromised QoL as compared to healthy controls: Integral QoL Index (IQoLI) – 0.283 vs 0.505 ($p < 0.001$); the worst QoL was observed for *physical functioning* and *role functioning* ($p < 0.001$). The majority of pts (98%) had LC symptoms; the most common and severe were fatigue and shortness of breath. After 2 cycles QoL improvement was registered in 51% of pts (Mean IQoLI increased by 59%); fatigue decreased in 43% of pts; shortness of breath – in 32%. Efficacy was evaluated in 112 pts (median first evaluation – 9.4 weeks): PR – 7%, SD – 45%, PD – 48%. 13 pts died before first efficacy evaluation. 47 pts were not evaluated for response on cut-off. In the group of pts who completed Nivo treatment (n = 106) median PFS – 2.5 mos (95%CI 2.2–2.9), median OS – 8.4 mos (95%CI 6.0–10.8); median follow-up – 17.4 weeks. AEs were registered in 51 pts (median of Nivo treatment – 12.4 weeks); among them 12 had grades 3-4 AEs.

Conclusions: Early data from this study supports the acceptable efficacy and safety of Nivo (7% of pts with 3-4 grades AEs) in NSCLC pts. Nivo treatment is accompanied with noticeable QoL improvement in 51% pts.

Legal entity responsible for the study: Multinational Center for Quality of Life Research

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Disclosure: T. Ionova: Principal Investigator of ISR sponsored by BMS. All other authors have declared no conflicts of interest.

1318P Italian nivolumab expanded access programme in non-squamous non-small cell lung cancer patients: Real-world results in never smokers and EGFR positive patients

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Background: Nivolumab is the first checkpoint inhibitor approved for the treatment of non-Squamous non-small cell lung cancer (non-Sq-NSCLC). In previous studies, a greater clinical benefit was shown in current and former smokers than in never smokers and in EGFR mutated patients (pts). Nevertheless, no data are available from a real-world setting. Here we report the data from Italian expanded access program (EAP) in the never smoker pts and EGFR mutated pts.

Methods: Nivolumab was provided upon physicians' request for pts aged ≥18 years who had relapsed after a minimum of one prior systemic treatment for stage IIIB/stage IV non-Sq-NSCLC. Nivolumab 3 mg/kg was administered intravenously every 2 weeks for ≤24 months. Pts included in the analysis received ≥1 dose of nivolumab and were monitored for adverse events (AEs) using Common Terminology Criteria for Adverse Events.

Results: Of 1588 patients with non-Sq-NSCLC, 305 (19%) were never smokers and, among 1455 pts evaluable for EGFR mutation, 102 (7%) were positive. In the never smoker group, EGFR status was available for 287 pts, with 51 (19%) who harbored an activating EGFR mutation. Among never smokers, with a median follow-up (FU) of 7.0 months (0.1-20.3) and a median of 7 doses (1-38), the objective response rate (ORR), the disease control rate (DCR) and the median overall survival (OS) were 9%, 42% and 10.0 months (8.1-11.9), respectively. Among all EGFR positive pts, with a median FU of 5.5 months (0.1-20.9) and a median of 6 doses (1-40), the ORR, DCR and median OS were 9%, 30% and 8.3 months (2.2-14.4), respectively. In the never smoker group, EGFR positive pts had 2% ORR, 26% DCR and 5.6 months (3.4-7.8) of median

OS. However, it should be considered that these pts had poorer prognostic factors (ECOG performance status, brain metastasis) at baseline.

Conclusions: These preliminary results represent the first real-life data regarding the efficacy of nivolumab in special subpopulations, including never smokers and EGFR positive pts. Even if ORR and OS seem lower than in general population, due to lack of alternatives and good safety profile, nivolumab should be considered as a therapeutic option.

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1319P Efficiency of nivolumab in the treatment of second-line advanced non-squamous non-small cell lung cancer (NSCLC) in Spain

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Background: The aim was to estimate the cost per life year gained (LYG) and quality-adjusted life year (QALY) of nivolumab compared to the standard of care, docetaxel, as second-line (2L) treatment in advanced non-squamous (NSQ) NSCLC patients in Spain.

Methods: An economic model with 3 health-states: progression free (PF), progressive disease (PD) and death was used to simulate, for a lifetime horizon, the total costs (€,2016) and clinical evolution of 1,000 NSQ NSCLC patients, treated with nivolumab or docetaxel. PF survival (PFS) and overall survival (OS) Kaplan-Meier curves, derived from CheckMate 057 trial, were used for monthly modelling of patient survival. Adverse event (AE) frequency and quality of life (utilities) were derived from CheckMate 057. PD implied the administration of one subsequent treatment (3L, defined by local oncologists). Costs relevant for the National Health System were included: acquisition drug costs (for 2L and subsequent treatments) using public list prices (confidential reimbursed price was used in an alternative analysis), administration, Grade 3-4 AE management, monitoring, and follow-up disease management at PF, PD and "end of life" care. Dosages for both therapies were derived from Summary of Products Characteristics. Costs and outcomes were discounted (3% annually). Unitary costs were obtained from a national costs database. Resources consumption for AE, disease management and pattern for 3L were defined by local oncologists. Sensitivity analyses (SA) were performed to verify the model robustness.

Results: Nivolumab was more effective than docetaxel, yielding 0.96 LYG and 0.81 additional QALY per patient. Total cost was higher with nivolumab (increment of €31,656), mainly driven by 2L drug and follow-up cost. Incremental ratios were €41,431/LYG and €45,738/QALY at public list prices (33,047€/QALY at reimbursed prices). In the probabilistic SA 92.5% of iterations resulted <€45,000/QALY gained at reimbursed prices.

Conclusions: Considering a willingness-to pay threshold of €30,000-€45,000/QALY gained, nivolumab versus docetaxel could be considered a cost-effective option for 2L treatment in Spanish patients with NSQ NSCLC.

Legal entity responsible for the study: Bristol Myers Squibb

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1320P Use of nivolumab in elderly patients with advanced non-squamous NSCLC: Results from the Italian expanded access program (EAP)

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Background: The efficacy and safety of nivolumab in patients with non-squamous non-small cell lung cancer (Non-Sq-NSCLC) have been demonstrated in several trials including the phase 3, randomized, controlled CheckMate 057 study which led to the approval of the product for this indication. However, data on the use of nivolumab in the real-BVLworld setting is still limited. The Italian nivolumab EAP for Non-Sq-NSCLC represents an important source of information. The current analysis describes results of the use of nivolumab in the group of EAP patients (pts) aged >70 and >75 years.

Methods: Nivolumab was available upon physician request for pts aged ≥18 years who had relapsed after a minimum of one prior systemic treatment for stage IIIB/IV Non-Sq-NSCLC. Nivolumab 3 mg/kg was administered intravenously every 2 weeks to a maximum of 24 months. Pts included in the analysis had received ≥ 1 dose of nivolumab and were monitored for adverse events (AEs) using Common Terminology Criteria for Adverse Events.

Results: Of 1588 Italian pts with advanced non-Sq-NSCLC participating in the EAP in Italy, 522 (33%) were ≥70 years and 232 (15%) were ≥75 years. The median follow up was 7.6 months (0.1-20.8) and 8.3 (0.1-20), respectively. For pts aged ≥70, median number of doses was 9 (1-44) and the disease control rate (DCR) was 48%, including 2 pts with a complete response (CR), 106pts with a partial response (PR) and 145 with stable disease (SD). For pts aged ≥75, median number of doses was 11 (1-39) and the DCR was 53%, including 58pts with a PR and 64 with SD. Among pts aged >70, 403 discontinued treatment for any reason, with only 25 (5%) discontinuation due to related AEs vs 177 discontinuation for any reason, with only 13 (6%) due to related AEs among pts aged >75. As of March 2017, median overall survival was 11.5 months (10.0-13.0) and 12.0 months (9.2-14.8) respectively in ptsaged ≥70 and ≥75. The efficacy, safety and drug-related discontinuation results are in line with what observed in the general population.

Conclusions: These results suggest that elderly population receive similar benefit from nivolumab treatment both in term of efficacy and safety than younger patients, supporting the use of nivolumab in this subpopulation.

Legal entity responsible for the study: Bristol-Myers Squibb

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Disclosure: All authors have declared no conflicts of interest.

1322P Real life experience with nivolumab in patients (pts) with advanced non-squamous NSCLC (nSq-NSCLC) exhibiting KRAS mutations: The Italian Expanded Access Program (EAP)

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Background: Nivolumab has been approved by different regulatory agencies worldwide for the treatment of nSq-NSCLC based on its superiority in Overall Survival (OS)

versus docetaxel in CheckMate 057 trial. In a pre-specified subgroup analysis of the same trial, this advantage was confirmed also in *KRAS*-mutation+ pts but the small number precluded any definitive conclusion. The Italian nivolumab EAP for non-sq-NSCLC might represent an important source of information in that respect. The current analysis describes results of the use of nivolumab in the group of EAP pts with *KRAS* mutations.

Methods: Nivolumab was provided upon physicians' request for pts aged ≥18 years who had relapsed after a minimum of one prior systemic treatment for stage IIIB/stage IV non-Sq-NSCLC. Nivolumab 3 mg/kg was administered intravenously every 2 weeks for ≤24 months. Pts included in the analysis received ≥1 dose of nivolumab and were monitored for adverse events (AEs) using Common Terminology Criteria for Adverse Events.

Results: In total, 1588 Italian pts with advanced nSq-NSCLC received at least one dose of nivolumab in the EAP across 168 sites. Among pts evaluated for *KRAS* mutation, 206 (39%) resulted positive. In this subgroup of pts, with a median follow-up of 7.7 months (0.1-21.2) and a median number of 8 doses (1-45), the best overall response rate (BORR) was 20%, including 2 pts with complete response and 39 pts with partial response, and the median OS was 10.7 months (8.6-12.8). These results were in line with those ones showed in the overall population (18% BORR and 11 months median OS, respectively).

Conclusions: This analysis confirms, in a real word setting and in a much larger number of pts, the efficacy of nivolumab in *KRAS*-positive pts in CheckMate 057. Nivolumab represents a potentially effective therapeutic option for *KRAS* mutation, a molecular alteration for which there is currently no direct targeted therapy.

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1323P Baseline corticosteroids (CS) could be associated with absence of benefit to immune checkpoint inhibitors (ICI) in advanced non-small cell lung cancer (NSCLC) patients

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Background: Concomitant use of corticosteroids (CS) during immune checkpoint inhibitors (ICI) therapy are not recommended, but their real impact on ICI efficacy remains unknown. The aim of this study was to assess the impact of CS on ICI outcomes in NSCLC pts.

Methods: Baseline CS intake and dose, patient characteristics and outcome were retrospectively collected in patients treated with PD1/PDL1 inhibitors from Nov. 2012 to Mar. 2017 in our Institute. Primary endopoints were overall survival (OS) and disease control rate (DCR: complete response + partial response + stable disease) and secondary endpoint was progression free survival (PFS).

Results: We enrolled 244 pts. Median age was 63 years (30-85), 158 (65%) were males, 212 (87%) smokers, 196 (80%) PS 0-1; 155 (64%) had non-squamous cells carcinoma. The median of prior lines was 1 (0-11). KRASmut and EGFRmut was present in 62 (25%) and 14 (6%) of NSCLC, 3 (1%) were ALK+, 64 (26%) PDL1 + (cut-off 1% of tumor cells), 24 (10%) PD-L1- and 156 (64%) PD-L1 unknown. In the whole population, the overall response rate (ORR) was 20% and DCR 50%. Median OS and PFS were 9 months (m) [6-12] and 2m [2-3], respectively. The median follow-up was 10m [7-12]. Sixty-six patients (27%) received CS at baseline. Main reasons for taking CS were dyspnea (48%) and brain metastasis (15%). The median dose of daily prednisone was 16.25 mg [5;32.75] and >20mg in 19 (29%). CS dose >20mg was an independent factor for poor OS [HR 1,013, 95% CI 1,006; 1,02, p < 0,0001). For patients taking CS > 20mg, the median OS was 3m [2-12] vs. 10m [7-15] for <20mg (p = 0.005). The median PFS for >20mg was 1m [1-4] vs. 3m [2-4] for < 20mg (p = 0.002). CS > 20mg was also significantly associated with progressive disease (p = 0.011).

Conclusions: Baseline daily prednisone intake of at least 20mg is associated with poor outcomes in advanced NSCLC treated with ICI. Further prospective studies are awaited for validating the real impact of CS in ICI efficacy.

Legal entity responsible for the study: Dr Benjamin Besse

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1324P Practical effectiveness efficacy and safety of nivolumab for advanced non-small cell lung cancer: A retrospective multicenter analysis

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Background: Nivolumab, an immune checkpoint inhibitor, is now a standard treatment for previously treated advanced non-small cell lung cancer. We aimed to evaluate the real-world efficacy and safety of nivolumab in a non-selective population and identify clinical characteristics that influence efficacy.

Methods: One hundred and forty-two patients with previously treated advanced non-small cell lung cancer who were administered nivolumab at Keio University and affiliated hospitals (in Japan) between January and July 2016 were enrolled. Treatment responses and adverse events were retrospectively reviewed and clinical characteristics associated with nivolumab responses were evaluated using univariate and stratified analyses and the Cochran-Mantel-Haenszel test.

Results: The objective response rate was 17.0%, while the proportion of patients with adverse events of any grade was 45.0%. Clinical characteristics such as age, sex, Eastern Cooperative Oncology Group performance status, histological type, presence or absence of central nervous system metastases, smoking status, and the number of previous lines of treatment, were not related to efficacy. However, *EGFR*/*ALK* mutation status was inversely associated with treatment response ($P < 0.05$). Prior radiotherapy also exhibited a positive association with treatment response ($P = 0.012$). Although no significant difference was observed between current/ex-smokers and non-smokers ($P = > 0.05$), a subgroup analysis revealed smoking status in pack-years to be significantly higher in responders than non-responders ($P < 0.05$). Nivolumab is effective and safe regardless of age or the number of previous lines of treatment.

Conclusions: The objective response rate and adverse event profiles were comparable to those observed in previous clinical trials. An *EGFR*/*ALK* mutation-negative status and prior radiotherapy are key clinical characteristics that are statistically associated with a positive treatment response. Our findings may aid in the efficient immunotherapeutic management of advanced non-small cell lung cancer.

We will add other measurements of the treatment activity such as progression-free survival by the congress.

Legal entity responsible for the study: Keio University

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1325P Generalization and representativeness of phase III immune checkpoint inhibitor trials in NSCLC

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Background: Immune checkpoint inhibitors (ICBs) have become standard treatment in platinum-failed non-small cell lung cancer (NSCLC) based on several phase III studies. Recent randomized phase III trials have led to the approval of ICB. However, strict criteria for patient enrollment of phase III trials raise questions regarding generalization in the real world. The aim of this study was to evaluate whether pivotal phase III trials using ICB represent the real world NSCLC patients.

Methods: We reviewed the inclusion/exclusion criteria of 3 practice changing phase III trials (CheckMate057, CheckMate017, KEYNOTE-010). Availability of tumor tissue and other exclusion criteria for KEYNOTE-010 were additionally checked. We retrospectively analyzed the database of stage IIIB or IV NSCLC patients diagnosed from 2011 to 2013 at Seoul National University Hospital (cohort 1). We also analyzed the criteria in 53 NSCLC patients who have treated with nivolumab or pembrolizumab as a routine practice (cohort 2).

Results: Among the 715 NSCLC patients in cohort 1, 499 (69.9%) were ineligible for 3 trials. Reasons for ineligibility were as follows: no platinum doublet 23.6%, lack of tissue 22.7%, the Eastern Cooperative Oncology Group performance status > 1 14.1%, steroid use 18.2%, active central nervous system metastasis 8.3%, hepatitis B or C virus/human immunodeficiency virus 8.0% and no measurable lesion 7.3%. EGFR mutation was more common in ineligible group than eligible group (44.7% vs 19.7%, P < 0.001) In cohort 2 which comprise 53 patients who received ICB as a routine practice, 67.9% were classified as ineligible group. Treatment outcomes of ICB in cohort 2 seems to be inferior than those of 3 trials: response rate of 11.3%, disease control rate of 26.4%, and median progression-free survival of 1.67 months.

Conclusions: Only 30.2% of NSCLC patients were eligible for ICB phase III trial. Although ICB have approved for all platinum-failed NSCLC, the real world efficacy of 60% ineligible patients were still unknown. These findings suggest that a huge gap between the practice changing phase III trials and real world NSCLC patients.

Legal entity responsible for the study: Bhumsuk Keam

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1326P Long-term follow-up results of stage III-IV non-small-cell lung cancer (NSCLC) patients treated with an epitope derived from Indoleamine 2,3 Dioxygenase (IDO) in a phase I study

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Background: A long-term follow up on an earlier published clinical trial of 15 stage III-IV NSCLC patients treated with and IDO peptide vaccine.[1]

Methods: 15 patients with stage III-IV NSCLC in disease stabilization after standard chemotherapy were treated with subcutaneous vaccinations (100 µg IDO5 peptide, seq ALLEIASCL, in 900 µl Montanide). Patients were enrolled from 2010 to 2012 and treated biweekly for 2.5 months and thereafter monthly until progression or up to 5 years. As published in Clin Cancer Res 2013, the vaccine was well tolerated and a long-lasting PR + SD (>8.5 months) was seen in 47% of the patients. A long-term follow-up has been made, investigating the long term clinical benefit and immunity.

Results: 3 of the 15 patients are still alive (May 2017) corresponding to a 5-year overall survival of 20%. One was excluded due to progression after 11 months; the other two have continued vaccination for 5 years and have both received 56 vaccines in total. One of the two patients developed a partial response of target lesions in the liver 15 months after the first vaccine and has been in stable disease ever since. The other patient had a solitary metastasis in a retroperitoneal gland at baseline and at the 1st evaluation scan the patient had no sign of malignancy and has been tumour free ever since. The vaccine was well tolerated for all 5 years. Analyses of PBMCs every 3rd to 6th month during treatment of the two long-term responders demonstrated a stable CD8+ T-cell population. The percentage of NK cells, MDSCs and Tregs were stable over time, demonstrating no sign of toxicity of the immune cells in the blood. Presence of IDO-specific $CD8^+$ T cells were demonstrated by IFN-γ Elispot and could be detected in both patients at several time points during vaccinations.

Conclusions: The vaccine was well tolerated with no severe toxicity for administration up to five years. Two of 15 patients are long-term survivors with ongoing clinical response five years after 1. vaccination. 1. Iversen, T. Z. *et al.* Long-lasting disease stabilization in the absence of toxicity in metastatic lung cancer patients vaccinated with an epitope derived from indoleamine 2,3 dioxygenase. *Clin. Cancer Res.* 20, 221–232 (2014).

Clinical trial identification: NCT01219348

Legal entity responsible for the study: Herlev and Gentofte Hospital, Center for Cancer Immune Therapy, Department of Hematology and Oncology, Denmark

Funding: IO Biotech, Denmark

Disclosure: All authors have declared no conflicts of interest.

1327P The Lung Immune Prognostic Index (LIPI), a predictive score for immune checkpoint inhibitors in advanced non-small cell lung cancer (NSCLC) patients

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Background: Derived NLR (neutrophils/(leucocytes-neutrophils) ratio) and lactate dehydrogenase (LDH) have been correlated to immune checkpoint inhibitors (ICI) benefit in melanoma. We tested whether baseline dNLR and LDH, as a score, could have the same role in advanced NSCLC patients.

Methods: Baseline dNLR and LDH were retrospectively collected in 466 patients treated with ICI from Nov. 2013 to Jan. 2017, in a training cohort (N = 161) and a validation cohort (N = 305) from 8 European centers. As a control, a cohort (N = 162) treated only with chemotherapy between Nov. 2012 and Jul. 2016 from 2 centers. The primary endpoint was overall survival (OS), and secondary endpoints were progression free survival (PFS) and disease control rate (DCR).

Results: In the immunotherapy cohort, 301 patients (65%) were males, 422 (90%) smokers and 401 (87%) with PS ≤ 1, with median age 63 years; 270 (58%) had adenocarcinoma and 159 (34%) squamous; 85 (18%) were KRASmut, 19 (4%) EGFRmut and 6 (1%) ALK positive. PDL1 was ≥ 1% by immunohistochemistry in 96 (74%), negative in 33 (26%) and unknown in 337 patients. The median of prior lines was 1 (0-11). In the training cohort, the median PFS and OS were 3 months (m) [2-4] and 10m [8-13]. dNLR>3 and LDH> Upper Limit of Normal (ULN) were independent factors for OS (HR 2.22, 95% CI 1.23-4.01; HR 2,51, 1.32-4.76, respectively). According to dNLR>3 and LDH>ULN, LIPI categorized 3 groups (good: 0 factor, intermediate: 1 factor, poor: 2 factors), which correlated with outcome in both cohorts. Median OS for good, intermediate, and poor was 34m, 10m and 3m, respectively (p = 0.0001). The PFS and DCR were also correlated (p = 0.001, p = 0.005). Same results were observed in the validation cohort for OS (p = 0.004), PFS and DCR (both p = 0.005), but not in the chemotherapy cohort for both factors analyzed.

Conclusions: Baseline LIPI, combining dNLR>3 and LDH>ULN, predicts the resistance to ICI acording to OS, PFS and DCR, but it is not correlated with the efficacy of chemotherapy, suggesting LIPI as a predictive score in ICI treatment.

Legal entity responsible for the study: Prof Benjamin Besse

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Disclosure: J-C. Soria: Consultancy fees from AstraZeneca, Astex, Clovis, GSK, Gammamabs, Lilly, MSD, Mission Therapeutics, Merus, Pfizer, Pharmamar, Pierre Fabre, Roche-Genentech, Sanofi, Servier, Symphogen, Takeda. All other authors have declared no conflicts of interest.

1328P Association of single nucleotide polymorphisms with efficacy in nivolumab-treated NSCLC patients

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Background: Proper patient selection for PD-1 checkpoint inhibitors is crucial given its limited efficacy in the majority of patients. We previously showed that a single nucleotide polymorphism (SNP) in the auto-immunity (AI) related *PTPN11* gene (rs2301756) is associated with increased toxicity on nivolumab (Bins et al, ESMO immuno-oncology symp, 2016). The objective of the current analysis was to assess whether SNPs in *PTPN11* and other genes associated with AI, which are putatively considered important in PD-1 influenced T-cell responses, are correlated with treatment efficacy of nivolumab in NSCLC patients.

Methods: The association between 5 SNPs and efficacy was evaluated in 161 (chemotherapy pretreated) advanced NSCLC patients. Efficacy measures included early progressive disease (PD; ≤ 90 days after start), tumor response according to RECISTv1.1, PFS and OS. The SNPs were located on 4 genes, being *PDCD1*, *PTPN11*, *ZAP70* and *IFNG*, respectively, encoding for the proteins PD-1, SHP-2 and ZAP70 and IFN-γ. The best model for every SNP, being either a dominant, recessive, multiplicative or additive model, was selected. SNPs were analyzed in multivariable logistic regression models if they showed a p-value <0.1 in univariable analysis, and were corrected for age and gender. PFS and OS analysis was done using the Kaplan-Meier method.

Results: Overall, 54 patients showed PR or CR according to RECIST. Patients with at least one variant allele in *PTPN11* had a higher response rate compared to wild-type (50% vs 30%; OR 2.4; 95% CI 1.0 – 5.5; p = 0.042). Other SNPs were not associated with response rate, and none of these SNPs were associated with early PD. Until the day of analysis, at which 128 patients had PD and 107 patients were dead, none of the SNPs was associated with PFS or OS.

Conclusions: Our results show that the SNP in *PTPN11* predisposes for a higher response rate to nivolumab therapy. Together with our earlier finding that this SNP is associated with grade ≥ 3 toxicity, this may indicate that SHP-2 activity influences treatment outcome of anti-PD-1 therapy in terms of both toxicity and anti-tumor effects. If confirmed, SNPs in *PTPN11* should be considered to be included as a biomarker in routine analysis of NSCLC patients to be treated with nivolumab.

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Funding: None

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1329P Systematic inflammation and histologic grade in non-small cell lung carcinoma

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Background: Tumor grade is an important factor of cancer outcome. Systematic inflammation has been associated with tumorigenesis and tumor aggressiveness and prognosis in several human malignancies. Cancer cells create an inflammatory peritumoral microenviroment by releasing a number of cytokines.

Methods: In total, 100 patients (88 males) with histologically proven NSCLC and no signs of active infection were evaluated. Tumor grade was examined and systematic inflammatory response was assessed by circulating levels of C-reactive protein (CRP), albumin, ferritin, transferring and the modified Glasgow Prognostic Score (mGPS). Patients were followed up and survival data were subsequently collected. Associations with clinicopathological, histological parameters and patients' survival were studied.

Results: Histological grade was associated with tumor size, the presence of pathological lymph nodes, organ metastases and advanced disease stage ($p = 0.010$, $p < 0.001$, $p < 0.001$ and $p < 0.001$, respectively). There was a trend of higher histological grade in adenocarcinomas compared to squamous carcinomas ($p = 0.263$). High tumor histological grade was also significantly associated with elevated serum CRP levels ($p < 0.001$), hypoalbuminemia ($p = 0.009$), elevated ferritin levels ($p = 0.049$), abnormal mGPS ($p = 0.006$) and a trend for reduced transferrin levels ($p = 0.101$). In multivariate analysis, histological grade, stage, ECOG performance status and mGPS were identified as independent prognostic factors for overall survival (Cox regression analysis, $p = 0.002$, $p = 0.001$, $p = 0.010$ and $p = 0.019$, respectively).

Conclusions: Our data support the association of tumour grade with the presence of systemic inflammation; two well described negative prognostic factors for NSCLC. To our knowledge this is the first time that these factors are associated with each other giving more information about the prognosis in patients with NSCLC.

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Funding: None

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1330P Impact of next generation TKI and co-occurring mutations in ALK-positive NSCLC patients: Results of the Network Genomic Medicine

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Background: Anaplastic lymphoma kinase (ALK) gene rearrangements define a molecular subtype of 3-4% of non-small-cell lung cancer (NSCLC), highly sensitive to therapy with ALK-directed tyrosine kinase inhibitors (TKI). Genetic heterogeneity of ALK-positive lung cancer patients (pts) is poorly characterized due to the lack of multiplex diagnostics results besides conventional FISH diagnostics. The Network Genomic Medicine (NGM) performs next generation sequencing (NGS) based diagnostics on a central platform in Cologne for advanced lung cancer pts in Germany.

Methods: The NGS panel used in NGM consists of 17 genes covering potentially targetable aberrations and is run on an Illumina (MySeq) platform. In 2016, we have started retrospective evaluation of ALK-positive NGM pts with available clinical data from the time period before and after NGS implementation. In particular, we have focused on ALK-positive NSCLC pts treated with chemotherapy, crizotinib and next generations TKI. Furthermore, we have analyzed the impact of co-occurring mutations: their frequency, significance and impact on overall survival.

Results: We have analyzed 289 ALK-positive pts with eligible clinical data. Co-occurring mutations were detected in 31% of these pts. The most frequent co-alteration was mutated TP53 in 23% of the ALK-positive patients. Regardless of the treatment regime, pts without co-occurring mutations seem to have a better overall survival (OS) with 37 versus (vs.) 15 month in pts with co-mutations ($p = 0.038$). TP53 co-mutated pts show an OS of 10 month ($p = 0.004$). Likewise, next generation TKI treatment exerts a highly positive impact on overall survival compared to chemotherapy and crizotinib treatment: 50 vs. 11 vs. 31 month ($p > 0.0001$).

Conclusions: While the first NGM evaluation in 2013 already showed a survival benefit of pts with activating genetic aberrations in EGFR and ALK, our current evaluation shows the heterogeneity of ALK-positive lung cancer pts and, for the first time to our knowledge, the impact of co-occurring mutations in these pts cohort. This work provides evidence for the efficacy of sequential ALK inhibitor treatment using next generation inhibitors and underlines the relevance of multiplex genotyping.

Legal entity responsible for the study: University Hospital of Cologne for the Network Genomic Medicine

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1331P Detection of EGFR T790M in Asia-Pacific patients (pts) with EGFR mutation-positive advanced non-small cell lung cancer (NSCLC): Circulating tumour (ct) DNA analysis across 3 platforms

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Background: Osimertinib is an oral, potent, CNS active, irreversible EGFR-TKI approved to treat pts with T790M-positive NSCLC. Non-invasive methods to confirm presence of T790M are needed to identify pts who could benefit.

Methods: AURA17 (NCT02442349) is a Phase II, single arm study investigating the safety and efficacy of osimertinib 80 mg once daily in an Asia-Pacific pt population with T790M positive advanced NSCLC, who had disease progression following EGFR-TKI therapy. Tumour tissue T790M status was centrally confirmed by **cobas**® EGFR Mutation Test (Roche Molecular Systems). Where possible, matched plasma ctDNA samples collected at screening were analysed for EGFR mutations using 3 tests: **cobas**® EGFR Mutation Test v2.0 (cobas plasma), AmoyDx SuperARMS EGFR T790M Mutation Detection Kit (SuperARMS) and droplet digital PCR (ddPCR; in-house research assay).

Results: Table summarises concordance data.

Table: 1331P Sensitivity and specificity of plasma tests using cobas tissue test as the reference

% (95% CI)		cobas plasma (n = 240)	SuperARMS (n = 249)	ddPCR (n = 249)
T790M	PPA	42 (34, 50)	49 (41, 57)	56 (48, 64)
	NPA	83 (72, 91)	78 (67, 86)	73 (62, 83)
L858R	PPA	65 (54, 75)	NA*	62 (51, 72)
	NPA	100 (98, 100)	NA*	99 (96, 100)
Exon 19 deletions	PPA	86 (80, 92)	NA*	66 (58, 74)
	NPA	97 (91, 99)	NA*	98 (93, 100)

NPA, negative percent agreement (specificity); PPA, positive percent agreement (sensitivity); *SuperARMS used solely for detection of T790M Number of patients tested with cobas tissue test: 277 In the evaluable for response (EFR; 4 March 2016 data cut-off) set, pts with T790M-positive status by both tumour and plasma analysis had confirmed objective response rates (ORR) with osimertinib (RECIST 1.1 by blinded independent central review) of 56% (95% CI 43, 69; 36/64 pts) using cobas plasma, 64% (52, 74; 49/77 pts) using SuperARMS, and 56% (45, 67; 49/87 pts) using ddPCR. ORR in the overall EFR tumour T790M-positive population was 60% (52, 68; 100/166 pts).

Conclusions: Using cobas tissue test as the reference, sensitivity for plasma T790M detection slightly increased with superARMS and ddPCR compared to cobas plasma test. Conversely, specificity slightly decreased. In pts with tumour T790M positive status, ORR with osimertinib was consistent across plasma tests, and with the overall tumour T790M-positive population. Biopsy is recommended for pts with a plasma T790M-negative test result, where feasible.

Clinical trial identification: NCT02442349

Legal entity responsible for the study: AstraZeneca

Funding: AstraZeneca

Disclosure: C. Zhou: Lecture honorarium: Eli Lily, AstraZeneca, Roche, Pfizer, Sanofi, Boehringer Iingelheim, Henrui Advisory Board: Roche, Boehringer Ingelheim, AstraZeneca. Y. Cheng: No financial interest in products or processes involved in our research. X. Ye, Y. Sun, X. Huang: Employee of AstraZeneca. S. Patel: Employee of, and shareholder in, AstraZeneca. Y-L. Wu: Speaker fees from AstraZeneca, Roche, Eli Lilly, Sanofi, Pfizer. All other authors have declared no conflicts of interest.

1332P Influence of plasma T790M mutation on clinical decision after 1st generation EGFR-TKI resistance in a Real-world study

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Background: T790M mutation detection in circulating tumor DNA (ctDNA) has shown great potential in clinical application. However, few studies reported the influence of plasma T790M mutation on selection of clinical treatment and survival time after first generation TKI resistance.

Methods: 307 patients with advanced or recurrent NSCLC who had progressed during EGFR-TKIs treatment were enrolled prospectively (NCT02418234) from March 2015 to March 2016. Blood samples were drawn within two weeks from PD occurred. T790M mutations were evaluated by droplet digital PCR. We undertook follow-up every 3 months by phone till April 2017. The median follow-up time was 11 months (range, 2 to 22 months).

Results: Our results showed that the median survival time after TKI progression was 17.5 months (95%CI, 15-20 months) and six kinds of treatments were used in these patients, including continuation of TKI (27.0%), AZD9291 (27.7%), chemotherapy with or without radiotherapy (15.3%), TKI combined with chemo/RT (6.5%), switch to another TKI (2.6%) and best supportive care (11.4%). 88.6% of patients received subsequent treatment. T790M- patients were likely to receive continuation of original TKIs, which accords for 29.5% (52/176), the percentage of switch to another TKI is the lowest (2.8%, 5/176). In T790M+ patients, AZD9291 is the first choice as the subsequent treatment, which accords for 38.9% (51/131). Switch to another TKI (2.2%, 3/131) and TKI combined with chemo/RT (6.1%, 8/131) is the least selection. Although most T790M- patients received continuation of original TKIs, combination of TKI and chemotherapy/radiotherapy seems to be a better choice, which got the longest survival than other treatment. For T790M+ patients, patients who choose AZD9291 had the longest survival.

Conclusions: T790M status in ctDNA have the great influence on clinical decision of the subsequent treatment, AZD9291 is the most frequent choice for the plasma T790M+ patients, which contributed the longest survival after 1st generation EGFR-TKI resistance.

Clinical trial identification: NCT02418234

Legal entity responsible for the study: Shenglin Ma

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Disclosure: All authors have declared no conflicts of interest.

1333P Detectability of RET fusions by amplicon-based next generation sequencing in nationwide lung cancer genomic screening project: LC-SCRUM-Japan

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Background: RET fusions have been identified as a therapeutic target in non-small cell lung cancer (NSCLC). The establishment of molecular diagnostics for RET fusions is required for the development of molecular-targeted therapies for fusion-positive patients. We have operated molecular testing for various actionable gene alterations, including RET fusions, in our nationwide lung cancer genomic screening project in Japan (LC-SCRUM-Japan).

Methods: Since 2013, RET fusions were analyzed by multiplex RT-PCR, and fusion-positive samples were confirmed by break-apart FISH. Since 2015, an amplicon-based next generation sequencing (NGS) system, Oncomine™ Comprehensive Assay was also applied in our genomic screening.

Results: As of February 2017, 244 institutions across Japan were participating, and a total of 4015 lung cancer patients including 3392 non-squamous (Non-Sq) NSCLCs were enrolled into the LC-SCRUM-Japan. Of the Non-Sq NSCLCs, available samples for multiplex RT-PCR and NGS were 94% (3186/3392) and 90% (1671/1852), respectively. RET fusions were detected in 89 samples (2.8%), including 54 detected by NGS. The types of variants found were KIF5B-RET (n = 50, 56%), CCDC6-RET (n = 20, 22%) and undetermined (n = 19, 21%). Of the 54 RET fusion-positive samples by NGS, the positivity was confirmed using break-apart FISH in 35 (92%) of 38 available samples. Among the 1335 samples available for both RT-PCR and NGS, the concordance rate between the two assays for the detection of RET fusions were 0.99. The detection sensitivity and specificity of the fusions in NGS assay were 0.98 and 0.99.

Conclusions: Our nation-wide screening results revealed that this amplicon-based NGS assay showed high sensitivity and specificity for the detection of RET fusions and is clinically applicable for diagnosis of RET fusions in lung cancer.

Legal entity responsible for the study: National Cancer Center

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1334P A comparison of Bronchial Washing Fluid (BWF) and histologic samples in the analysis of EGFR mutation in NSCLC patients

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Background: The aim of the current study was to examine the clinical application of BWF samples in detecting epidermal growth factor receptor (EGFR) mutations in a large sample set of NSCLC patients.

Methods: In diagnostic bronchoscopic examinations, before or after biopsy to target lesions, subsequent bronchial washing by saline was performed. Thereafter, EGFR mutation testing for both supernatant and sediment of BWF and histologic tissues was performed via amplification refractory mutation system real-time PCR (ARMS RT-PCR) assay.

Results: A total of 127 cases of histologic and corresponding BWF samples of patients underwent bronchoscopy for suspected lung malignant tumor lesions on chest radiography were successfully obtained. Of these, 72 cases were pathologically confirmed to be NSCLC based on forceps biopsy samples and EGFR mutations were identified in 26 cases. In 70 of 72 cases, the results of EGFR mutation status were concordant for BWF and histologic samples, and the concordance rate was 97%. In 13 cases that were not pathologically diagnosed with NSCLC with forceps biopsy samples but other samples, five cases (38.46%) with EGFR mutated-type were detected by BWF. The overall EGFR mutation concordance rate between supernatant and sediment specimens was 100%. The detection of EGFR mutations with supernatant/sediment of BWF samples showed a sensitivity of 86.5%, a specificity of 100%.

Conclusions: This study demonstrates a clear comparison of supernatant/sediment of BWF samples and histologic tissues for EGFR mutation testing with largest clinical samples to date. Both supernatant and sediment of BWF samples showed high credibility and concordance via highly sensitive PCR analysis. BWF is considered a simple, rapid and effective alternative for histologic samples in EGFR mutation testing.

Legal entity responsible for the study: Zhongshan Hospital

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1335P EGFR T790M detection in TKI-naïve NSCLCs carrying sensitive EGFR mutations

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Background: To date, the frequency of EGFR T790M in TKI-naïve patients remains unclear, ranging from 2% to 80% depending on the sensitivity and specificity of the methods. In this study we aimed to identify the frequency of EGFR T790M in NSCLCs before TKI treatment, comparing the detection rate of three highly sensitive molecular methods.

Methods: Among 1100 NSCLCs (adenocarcinomas at stage IIIB or IV), we identified 130 NSCLCs with EGFR TKI-sensitive mutations, by MALDI-TOF mass spectrometry (MALDI-TOF MS) and Myriapod® Lung Status kit. The diagnostic performance in detecting de-novo EGFR T790M in these 130 tumors was evaluated comparing three methods, namely MALDI-TOF MS, Real Time AS-PCR (Easy®EGFR kit) and ddPCR™ (QX200 Droplet Digital PCR, PrimePCR™ Assays). Sensitivity and specificity of each method were defined by using a DNA reference standard set (Horizon). Limit of blank (LOB) of AS-PCR and ddPCR were determined by measuring replicates of 16 wild-type EGFR DNA samples obtained from peripheral blood lymphocytes and from formalin-fixed paraffin embedded (FFPE) normal lung tissues.

Results: Comparison of the three methods was possible for 91 of the 130 NSCLCs. Overall, we identified a total of 16 de-novo T790M in the analyzable tumors (18%). In detail, 4 cases were identified by MALDI-TOF MS and confirmed by AS-PCR and ddPCR. Two T790M-mutated cases were additionally detected by AS-PCR. ddPCR confirmed EGFR T790M in all these tumors and additionally identified 10 mutated cases. Most of mutated cases showed a mutant-allele frequency between 5% and 0.1%. Titration experiments using a DNA reference standard set demonstrated higher sensitivity of ddPCR (0.1%) than AS-PCR (1%) and MALDI-TOF MS (5%). Analysis of wild-type EGFR DNA from FFPE samples was crucial for the determination of LOB of ddPCR in order to maximize sensitivity, avoiding loss of specificity.

Conclusions: In this study, 18% of TKI-naïve NSCLCs show EGFR T790M mutation together with an EGFR activating mutation. Most of mutated cases showed a mutant-allele frequency between 5% and 0.1%. ddPCR is a robust method enabling the detection of mutant-allele frequencies as low as 0.1%. However, a careful preliminary evaluation of the specificity of this test is mandatory, especially when FFPE tissues are investigated.

Legal entity responsible for the study: Asst-Sette Laghi Ospedale di Circolo Varese

Funding: AstraZeneca

Disclosure: All authors have declared no conflicts of interest.

1336P ALK fusion variants detection by targeted RNA-next generation sequencing and clinical responses to crizotinib in ALK-positive non-small cell lung cancer

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Background: The aim of the present study was to assess the yields of an amplicon-based parallel sequencing (RNA-seq) assay for ALK fusion transcript variants detection in comparison with immunohistochemistry (IHC) and fluorescent in-situ hybridization (FISH) in a selected population of ALK-positive and ALK-negative non-small cell lung cancer (NSCLC) cases, and to evaluate the impact of the ALK variant on crizotinib efficacy.

Methods: Our population comprised fifty-three NSCLC cases positive for ALK by IHC and/or FISH and twenty-three ALK-negative samples. For the ALK-positive samples, a distinction was made between 'truly' IHC/FISH positive or 'truly' IHC/FISH negative samples, and the samples for which the IHC and/or FISH were equivocal (IHC) or borderline-positive (FISH).

Results: On the overall population, RNA-seq sensitivity and specificity were of 80% and 100%, respectively when IHC and FISH were combined and of 100% for both for 'truly' positive samples. Interestingly, this assay also appeared to be a promising rescue technique in equivocal and/or borderline-positive IHC/FISH cases. Moreover, when crizotinib efficacy was evaluated according to the type of ALK variant detected, better clinical outcomes were observed in crizotinib-treated patients with EML4-ALK v1/v2/ others variants compared to v3a/b variants. A lack of efficacy of crizotinib was noted in KLC1-ALK variants.

Conclusions: RNA-seq detects *ALK* rearrangements with a high sensitivity and specificity and may be particularly useful in equivocal/borderline-positive IHC/FISH cases. In addition, it offers a unique opportunity to identify *ALK* fusion variants and to evaluate their predictive value for ALK inhibitors efficacy.

Legal entity responsible for the study: Anne Mc Leer

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1337P A meta-analysis on epidemiology of ROS1 rearrangement in Asian and non-Asian population

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Background: ROS1 is now recognised as a definite molecular target in NSCLC.[1] Studies showed that ROS1 positive patients are significantly younger & more likely to be non-smokers.[2] Previous studies found epidermal growth factor receptor (EGFR) mutation in NSCLC was significantly higher in Asian population compared to non-Asian.[3] Objective of the study is to evaluate difference between epidemiological parameters of ROS1 rearrangements in Asian & non-Asian patients by performing meta-analysis.

Methods: We systematically searched databases like PubMed & e-journals since 2011. Statistical analysis for this study was done on 20 studies (11,665 patients) conducted globally & open source software R (version 3.3.2) was used for meta-analysis.

Results: Global prevalence of ROS1 rearrangement was 2% (95% CI: 0.016- 0.026) & it was higher in Asian [2.2% (95% CI: 0.016- 0.029)] than non-Asian [1.9% (95% CI: 0.012-0.027)] ($p = 0.92$). Mean age of Asian & non-Asian was 54.5 yrs & 59 yrs respectively. The prevalence rate in non-Asian females, was significantly higher [3.8% (95% CI: 0.011-0.078)] than non-Asian males [0.7% (0.003- 0.012)] ($p = 0.003$). Similarly, prevalence rate in Asian females [2.8% (95% CI: 0.019-0.038)] was higher than Asian males [2.1% (95% CI: 0.012-0.033)] ($p = 0.88$). Smokers in Asia were more likely to have ROS1 rearrangement [1.8% (95% CI: 0.005-0.037)] compared to non-smokers [0.6% (95% CI: 0.0004-0.0152)] ($p = 0.93$). Whereas, prevalence rate amongst non-smokers in non-Asia [7.1% (95% CI: 0.039-0.110)] was significantly higher than smokers [0.7% (95% CI: 0.002-0.007)] ($p = 0.008$). Clinical stage IV was more common in both population than other stages. In 5 out of 20 studies, ROS1 positivity was higher (3-12.5%) in enriched (EGFR-ve/ALK-ve) population [non-smokers 6.5% (95% CI: 0.046-0.083)] compared to overall population.

Conclusions: Our meta-analysis showed that ROS1 gene rearrangement was more prevalent in NSCLC, females, non-smokers & patients with clinical stage IV while there is no significant difference in Asians vs non-Asians. **References** 1] Bubendorf et al. Virchows Arch. 2016; 469:489–503. 2] Bergethon et al. JCO. 2012; 30(8): 863-870. 3] Expert Opin Pharmacother. 2015 Jun;16(8):1167-76.

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1338P EGFR mutation detection in plasma cell-free DNA correlates with clinical outcomes in non-small cell lung cancer

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Background: Cell-free DNA (cfDNA) testing of epidermal growth factor receptor mutations (*EGFR*mut) is being investigated as an adjunct for diagnosis and monitoring in non-small cell lung cancer (NSCLC) patients. The performance of various amplicon-based targeted next-generation sequencing (NGS) methods, both with and without error correction, is of high interest. Outcomes of error-corrected NGS in plasma EGFRmut testing have not been previously independently reported. We deployed an in-house amplification-refractory mutation system PCR (ARMS-PCR) assay in a prospective study, benchmarking its performance against two NGS platforms in a patient subset.

Methods: An ultrasensitive ARMS-PCR assay for hotspot *EGFR*mut was established, with detection limits between 0.02% and 0.1%. A total of 134 plasma samples were prospectively analysed from 68 patients with metastatic lung adenocarcinoma at diagnosis or progression, recruited between Jan 13-Apr 17 from 5 centres, with serial monitoring of plasma *EGFR*mut till radiologic progression in one centre. We further evaluated the performance of ARMS-qPCR assay, AmpliSeq Lung and Colon NGS assay and Oncomine Lung cfDNA NGS assay in 29 NSCLC and 20 healthy plasma controls.

Results: Concordance rate between cfDNA and tumor was 83.8%, with sensitivity 80.0%, specificity 94.4%, positive predictive value 97.6%, and negative predictive value 63.0%. Dynamic monitoring of plasma EGFRmut levels demonstrated rising levels a median of 2.1 months [0.9-3.9] before radiological progression. This detection also held true for tissue EGFRmut positive patients negative for plasma EGFRmut at study entry. 20 of 49 patients at progression were plasma T790M-positive, and clinical benefit rates were 91.0% for osimertinib-treated patients. Evaluation of ARMS-PCR and NGS platforms yielded an average concordance rate, sensitivity and specificity was 85.9%, 63.4%, 92.3% (ARMS-qPCR), 87.2%, 47.8%, 100% (Ampliseq) and 84.1%, 83.1%, 87.4% (Oncomine).

Conclusions: ARMS-PCR provides a useful diagnostic and monitoring adjunct for NSCLC EGFRmut patients. Amplicon-based targeted next-generation sequencing approaches with error correction is a promising approach requiring additional validation.

Legal entity responsible for the study: Institute of Bioengineering and Nanotechnology

Funding: Agency for Science, Technology and Research (A*STAR)

Disclosure: All authors have declared no conflicts of interest.

1339P A large prospective cohort study of the clinical features of advanced lung cancer harboring HER2 aberrations (HER2-CS STUDY)

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Background: HER2 is a potential driver oncogene. HER2-targeted precision therapy has been tested in NSCLC. However, the demographics of HER2-positive NSCLC have not been defined systematically.

Methods: Pts with advanced NSCLC were registered. HER2-IHC and FISH assays were performed with commercial kits. HER2 mutations were identified by the direct sequencing. The aim of this study was to clarify the frequency, characteristics and outcome of HER2-positive NSCLC.

Results: Of 1,126 tumors screened (Table A), 34 (3.0%) were IHC3+, and 34 (3.0%) were IHC2+/FISH+. Among the 724 EGFR wild-type tumors, 21 (2.9%) were HER2-mutant tumors, including A775_G776insYVMA (n = 15). Interestingly, the IHC3+ tumors and mutant tumors were entirely exclusive. Female pts had HER2 mutant tumors more frequently, while IHC/FISH+ tumors were detected more often in males (Table B). HER2-positive tumors had similar survival outcome to triple negative tumors, but significantly worse prognoses than EGFR-mutant and ALK-positive tumors ($p < 0.05$ each).

Conclusions: This is the first prospective study showing a small fraction of NSCLC possessed HER2 aberrations. HER2-positive tumors had relatively poor prognosis. NSCLCs with HER2 IHC3+ and mutation seemed to be distinct subsets.

Clinical trial identification: UMIN registration number 000017003

Legal entity responsible for the study: HER2-CS Network

Funding: Japan Agency for Medical Research and Development

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1340P Transcriptomic analysis of bronchoalveolar lavage cells from advanced non-small cell lung cancer identifies overexpressed immunoglobulin genes of immunosuppressive implication

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Background: Diverse pattern of inflammatory cells infiltration in the microenvironment of non-small cell lung cancers (NSCLCs) has key implication for successful immunotherapeutic approaches (*Gajewski et al. Nat Immunol 2013*). However, study of these cells remains challenging particularly in advanced disease where tumor resection is never possible. We hypothesized that transcriptomic study of bronchoalveolar lavage (BAL) cells is useful in this setting to identify characteristic gene expression of immunological significance.

Methods: BAL cells were obtained from 13 patients of advanced NSCLC and 6 normal controls. In NSCLC group, lavage was performed from the lung segment where tumor was located. RNA was extracted and hybridized to Affymetrix HG-U133 plus2

Table: 1339P

A. The Genotype-Specific Subsets*

	HER2 (n = 88)	EGFR (n = 358)	ALK (n = 44)	Triple negative/ unknown (n = 664)	Total (n = 1,126)
Age, median Sex (male) Smoking habit Non-Sq Stage III/IV	69 61 (69%) 58 (66%) 78 (89%) 51 (58%)	69 142 (40%) 142 (40%) 351 (98%) 220 (61%)	62 21 (48%) 19 (43%) 44 (100%) 35 (80%)	69 516 (78%) 544 (82%) 503 (76%) 423 (64%)	69 726 (64%) 754 (67%) 951 (84%) 714 (63%)
MST (mo) 1-yr OS rate	17.5 59%	NR 85%	NR 79%	15.1 59%	19.8 67%

B. The Subsets of HER2 aberrations**

	IHC3 + (n = 34)	IHC2+/FISH + (n = 34)	Mutant (n = 21)
Age, median Sex (male) Smoking habit Non-Sq Stage III/IV	71 27 (79%) 24 (71%) 30 (88%) 17 (50%)	71 27 (79%) 26 (76%) 28 (82%) 21 (62%)	65 8 (38%) 9 (43%) 21 (100%) 14 (67%)
MST (mo) 1-yr OS rate	10.5 46%	16.0 70%	NR 59%

*including 22 pts with HER2-positive tumors with EGFR mutations, 2 with both HER2- and ALK-positive tumors, and 2 had ALK-positive tumors with EGFR-mutations.

**1 had an IHC2+/FISH+ tumor with mutation.

transcriptomic microarray. Raw intensity data was normalized by Robust Multi-Array Average and analyzed for differential expressed genes (DEGs) using Bioconductor R limma package.

Results: A total 129 DEGs were identified whose gene ontology enrichment analysis revealed the top over-represented pathways as circulating immune complex (GO: 0042571, $p=2.2x10^{-10}$), FCGR activation (REAC: 2029481, $p=5.4x10^{-11}$), and regulation of B cell activation (GO: 0050864, $p=2.4x10^{-5}$), in which a number of up-regulated genes encoding immunoglobulins, Src family kinases and interleukin (IL)-10 were noted. We integrated the immunoglobulin genes into a signature and calculated the enrichment score for each subject using Gene Set Variation Analysis (*Sonja et al. BMC Bioinformatics 2013*). Medium to high correlation of immunoglobulin signature with *IL-10* (Pearson's *r*: 0.64, $p=0.003$), with *FCGR2B* (Pearson's *r*: 0.43, $p=0.066$) and *FCGR2B* with *IL-10* (Pearson's *r*: 0.50, $p=0.029$) were determined. In addition, mild to medium correlation were identified between *IL-10* and Src family kinases *BLK* (Pearson's *r*: 0.48, $p=0.038$), *LCK* (Pearson's *r*: 0.40, $p=0.090$) and *YES1* (Pearson's *r*: 0.25, $p=0.300$).

Conclusions: Transcriptome of BAL cells around advanced NSCLCs showed characteristic expression of immunoglobulin signature that may implicate the immunosuppressive property in tumor milieu.

Legal entity responsible for the study: Chih-Hsi Scott Kuo MD

Funding: Chang Gung Medical Foundation

Disclosure: All authors have declared no conflicts of interest.

1341P Assessing response to immunotherapy in patients with non-small cell lung cancer using circulating tumor DNA

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Background: Evaluation of response to immune checkpoint inhibitors by serial imaging can be complicated by the possibility of pseudo-progression or delayed response, sometimes resulting in discontinuation of an effective therapy or delay of alternate treatment. Monitoring tumor cell death by measuring changes in circulating tumor DNA (ctDNA) levels in blood may permit early assessment of immunotherapy efficacy.

Methods: We examined ctDNA levels in plasma samples from patients with metastatic non-small cell lung cancer (NSCLC) undergoing treatment with a PD-1 or PD-L1 inhibitor. CtDNA was quantified in plasma by determining the allele fraction of cancer-associated somatic mutations using a multi-gene next-generation sequencing assay. A ctDNA response was defined as more than 50% decrease in mutant allele fraction from baseline, with a second confirmatory measurement. Radiographic response assessment was performed using RECIST 1.1. Changes in ctDNA levels over time were correlated with imaging findings and with clinical outcomes.

Results: Twenty-eight patients with metastatic NSCLC had ctDNA quantified in serial blood samples collected before and during treatment with a PD-1 axis inhibitor. Strong agreement was observed between ctDNA response and radiographic response (Cohen's Kappa = 0.753, $P < 0.001$). The median time to response was 24.5 days by ctDNA versus 72.5 days by imaging. Patients who had a ctDNA response remained on immunotherapy for a median of 205.5 days compared to a median of 69 days for those who did not have a ctDNA response ($p < 0.001$). Progression-free survival (PFS) and overall survival (OS) were significantly better for patients with a ctDNA response versus those without (hazard ratio [HR] for PFS, 0.29; 95% confidence interval [CI], 0.09-0.89; P = 0.03 and HR for OS 0.17; 95% CI, 0.05-0.62; P = 0.007).

Conclusions: An early drop in ctDNA level enables assessment of response to immune checkpoint inhibitor therapies at a time when radiographic response may be uncertain for patients with metastatic NSCLC. Achievement of such a ctDNA response is predictive of a longer duration of therapeutic benefit as well as superior PFS and OS.

Legal entity responsible for the study: Yale University

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1342P Detection of epidermal growth factor receptor mutations in circulating cell-free DNA versus tumor biopsy

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Background: Epidermal growth factor receptor (EGFR) mutations are predictive marker of EGFR-tyrosine kinase inhibitor (TKI) therapy. We compared the sensitivity of EGFR mutation detection techniques between matched tumor tissue and peripheral blood sample in patients with lung adenocarcinoma.

Methods: We collected the paired samples from plasma and paraffin-embedded tumor tissue in 295 patients before EGFR-TKIs therapy. DNA extraction was performed using the QIAamp MinElute virus spin kit and EGFR mutation analysis was done by two detection methods. One is the PNAClamp™ (Clamp) which is the PNA-based PCR clamping that selectively amplifies only the mutated target DNA sequence as minor portion in mixture with the major wild type DNA sequences. The other is the PANAMutyper™ EGFR kit (Mutyper), which use PNA clamping-assisted fluorescence melting curve analysis to perform mutation detection and genotyping.

Results: In tissue samples, the positive rates of EGFR sensitive mutation were not different between two methods (26.8% in Mutyper vs. 24.7% in Clamp). Plasma sensitivity was significantly higher in Mutyper than Clamp (70.9% vs. 30.1%, $p < 0.001$) with tissue as reference. The overall concordance and degree of agreement between two samples were better in Mutyper (91.2%, $k = 0.756$, $p < 0.001$) than Clamp (81.7%, $k = 0.369$, $p < 0.001$). The median progression-free survival (PFS) was significantly higher in EGFR sensitive group in tissue sample regardless of the two methods. In plasma sample, the median PFS of EGFR sensitive group was significantly longer than negative group only by Mutyper (11.8 vs. 3.7 months, $p = 0.020$), not by Clamp (9.8 vs. 11.0 months, $p = 0.968$).

Conclusions: The plasma sensitivity and concordance of Mutyper were better than Clamp test. And Mutyper could better predict the PFS of EGFR mutation in plasma. So this technique is expected to be useful to detect EGFR mutation in circulating cell-free DNA sample.

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1343P Efficacy and safety of lorlatinib in patients (pts) with ALK+ non-small cell lung cancer (NSCLC) previously treated with 2nd-generation ALK TKIs

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Background: Standard therapy for advanced anaplastic lymphoma kinase $(ALK)^+$ NSCLC consists of first-line crizotinib, followed by 2nd-generation ALK tyrosine kinase inhibitors (TKIs) such as ceritinib, alectinib, or brigatinib. While pts can achieve some clinical benefit from these agents, most will subsequently develop resistance. Lorlatinib, a brain-penetrant next-generation ALK TKI, is active against most known resistance mutations that can develop during treatment with 1st- and 2nd-generation TKIs. Here, we explore the antitumor activity and safety of lorlatinib in pts with ALK^+ NSCLC treated with ≥1 prior 2nd-generation TKI.

Methods: In this ongoing phase 2 study (NCT01970865), pts with ALK^+ or $ROS1^+$ NSCLC, ± asymptomatic untreated or treated central nervous system (CNS) metastases, were enrolled into 1 of 5 ALK^+ cohorts dependent on the number of prior TKIs received, and 1 $ROS1^+$ cohort with no restriction on the extent of previous therapy. Pts received lorlatinib 100 mg QD. The primary objective was overall and intracranial (IC) antitumor activity, measured as confirmed overall and IC response by independent central review (ICR).

Results: At the data cutoff (15 Aug 2016), 65 pts with ALK^+ NSCLC were treated with ≥1 prior 2nd-generation TKI (alectinib, ceritinib, brigatinib, or other). Of these pts, 41 had CNS metastases at baseline. The table shows the confirmed overall and IC responses (complete response + partial response) by ICR. The most common treatment-related adverse events (TRAEs) of any grade in pts who received prior ALK TKIs were hypercholesterolemia, hypertriglyceridemia, and peripheral neuropathy. Hyperlipidemia was successfully managed by appropriate medical treatment.

Table: 1343P

Type of 2nd-Generation TKI	Overall		Intracranial	
	N[a]	Confirmed Responses, n (%)	N[a]	Confirmed Responses, n (%)
Alectinib	33	9 (27)	16	8 (50)
Ceritinib	29	9 (31)	23	11 (48)
Brigatinib	6	1 (17)	3	0 (0)
Other	5[b]	2 (40)	4	2 (50)

[a]Patients in each group of prior TKI; a patient could have received more than one type of prior TKI.
[b]Other TKIs included entrectinib (n = 3) and ensartinib (n = 2).

Conclusions: Lorlatinib has shown clinical activity in pts with *ALK*$^+$ NSCLC who had received ≥1 prior 2nd-generation TKI.

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Legal entity responsible for the study: Pfizer

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1344P Brigatinib (BRG) in anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC): Long-term efficacy and safety results from a phase 1/2 trial

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Background: The next-generation ALK inhibitor BRG has shown activity in ALK+ NSCLC patients (pts) in clinical trials.

Methods: Pts with advanced malignancies (N = 137; including 79 pts with ALK+ NSCLC) received oral BRG (30–300 mg/d) in a phase 1/2, open-label, multicenter trial (NCT01449461). We report activity by RECIST v1.1 in ALK+ NSCLC pts and safety in all pts, with long-term follow-up (>31 months since last pt was enrolled).

Results: Among 79 ALK+ NSCLC pts, median age was 54 years; 90% (71/79) had received prior crizotinib (CRZ). As of 21 Feb 2017, 32% of ALK+ NSCLC pts (25/79) and 25% (7/28) of those receiving 180 mg qd with a 7-day lead-in at 90 mg (a regimen evaluated in the phase 2 portion of the trial) continued to receive BRG. Median treatment duration was 20.0 months (1 day to 56.1 months). Confirmed objective response rate (ORR) was 63% (45/71) in pts with prior CRZ and 100% (8/8) in CRZ-naive pts. Additional efficacy data are shown in the table. At 180 mg qd (with lead-in), confirmed ORR was 76% (95% CI, 55%–91%) and median progression-free survival (PFS) was 16.3 months (95% CI, 9.2–28.1) in pts with prior CRZ. Treatment-emergent adverse events (AEs) in ≥ 30% of all 137 pts, mostly grade 1/2, were nausea (55%), fatigue (45%), diarrhea (42%), headache (36%), and cough (34%). Grade ≥3 treatment-emergent AEs in ≥ 5% of pts were increased lipase (12%), pneumonia (7%), dyspnea (6%), and hypertension (6%). Eleven percent of pts (15/137) discontinued BRG due to an AE.

Conclusions: BRG shows major antitumor activity in ALK+ NSCLC pts with an acceptable safety profile in this long-term follow-up. PFS of > 16 months in pts receiving 180 mg qd with a 7-day lead-in at 90 mg is among the longest reported in CRZ-resistant ALK+ NSCLC. This dosing regimen is being investigated in a randomized phase 3 trial of BRG vs CRZ in ALK inhibitor–naive pts with advanced ALK+ NSCLC (ALTA-1L; currently recruiting pts).

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Table: 1344P

Efficacy in ALK+ NSCLC Pts

	With Prior CRZ			CRZ-Naive
	All n = 71	**90 mg qd[a] n = 13**	**90 mg → 180 mg qd[a,b] n = 25**	**All n = 8**
cORR, n (%) 95% CI	45 (63) 51–75	7 (54) 25–81	19 (76) 55–91	8 (100) 63–100
Median duration of response in confirmed responders, months 95% CI	14.5 9.0–26.1	11.1 3.8–16.7	14.9 7.9–33.3	32.4 5.6–NR
Median PFS, months 95% CI	13.2 9.2–16.7	11.9 3.5–21.2	16.3 9.2–28.1	34.2 7.4–NR
Probability of PFS at 1 year, % 95% CI	53 41–65	50 21–74	62 40–78	75 32–93
Median OS, months 95% CI	30.1 21.4–NR	21.2 9.9–47.6	29.5 21.4–NR	NR NR–NR
Probability of OS at 1 year, % 95% CI	77 65–85	69 37–87	84 63–94	100 100–100
Probability of OS at 2 years, % 95% CI	61 48–71	46 19–70	64 42–79	100 100–100

Time-to-event data reflect Kaplan-Meier estimates ALK+ NSCLC, anaplastic lymphoma kinase–positive non–small cell lung cancer; BRG, brigatinib; CI, confidence interval; cORR, confirmed objective response rate; CRZ, crizotinib; NR, not reached; OS, overall survival; PFS, progression-free survival; pts, patients
[a]BRG regimens used in the pivotal phase 2 trial
[b]180 mg qd with 7-day lead-in at 90 mg.

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1345P Intracranial efficacy of brigatinib (BRG) in patients (Pts) With crizotinib (CRZ)-refractory anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC) and baseline CNS metastases

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Background: The CNS is often a site of first disease progression in CRZ-treated ALK+ NSCLC pts; we report BRG efficacy and safety in pts with CRZ-refractory advanced ALK+ NSCLC in the phase 2 ALTA trial who had baseline CNS metastases.

Methods: ALTA (NCT02094573) permitted baseline CNS disease (including pts with prior whole brain radiotherapy/stereotactic radiosurgery and asymptomatic untreated pts). 222 pts stratified by presence of brain metastases and best response to prior CRZ were randomized 1:1 to receive BRG 90 mg qd (arm A, n = 112) or 180 mg qd with a 7-day lead-in at 90 mg (arm B, n = 110). This analysis included an exploratory competing risks analysis to estimate cumulative incidence of CNS progression vs non-CNS progression vs death in pts with baseline brain metastases.

Results: 80 (71%)/73 (66%) pts in A/B had baseline brain metastases per independent review committee (median age, 49/55 years; 76%/74% had received chemotherapy). As of 21 Feb 2017, median follow-up for pts with brain metastases was 17.7 months; 34%/40% continued to receive BRG in A/B. Table shows intracranial efficacy. 5 pts with measurable baseline brain metastases in A had progression in the brain (≥20% growth in target lesions or new lesions) while receiving BRG 90 mg qd and escalated to 180 mg qd with ≥1 additional scan; all 5 had a reduction in measurable lesions after escalation (−14% to − 100%). While pts without baseline brain metastases did not have routine brain MRI scans, 3/32 and 1/36 pts without baseline brain metastases per investigators in A and B, respectively, had a new brain lesion identified by MRI.

Conclusions: In this update of ALTA, BRG continued to show robust intracranial efficacy in ALK+ NSCLC pts with baseline brain metastases, particularly at 180 mg (with lead-in), with a higher intracranial response rate and a numerically lower incidence of disease progression in the CNS and outside the CNS, compared to 90 mg.

Table: 1345P

Intracranial Efficacy of BRG in Pts With CRZ-Refractory ALK+ NSCLC and Baseline Brain Metastases (per IRC)	**Arm A 90 mg qd**	**Arm B 90 mg → 180 mg qd[a]**
Confirmed iORR (pts with measurable brain metastases), n/N (%)	13/26 (50)	12/18 (67)
Confirmed iORR (pts with measurable, active[b] brain metastases), n/N (%)	9/19 (47)	11/15 (73)
Median duration of intracranial response[c] (pts with measurable brain metastases), months (95% CI)	NR (3.7–NR) n = 13	16.6 (3.7–16.6) n = 12
Median iPFS[c] (pts with any baseline brain metastases), months (95% CI)	12.8 (9.0–18.3) n = 80	18.4 (12.6–NR) n = 73
Competing risks analysis	n = 80	n = 73
CIR of first disease progression in CNS, % (95% CI)		
By 6 months	20 (12–29)	15 (8–25)
By 12 months	33 (23–44)	27 (17–37)
By 18 months	41 (30–52)	34 (23–45)
CIR of first disease progression at non-CNS site, % (95% CI)		
By 6 months	14 (7–23)	11 (5–20)
By 12 months	21 (13–31)	20 (11–30)
By 18 months	23 (15–34)	21 (13–32)
CIR of death prior to all disease progression (in CNS or at non-CNS site), % (95% CI)		
By 6 months	5 (2–12)	3 (1–9)
By 12 months	9 (4–17)	6 (2–13)
By 18 months	9 (4–17)	7 (3–15)

Pts with baseline brain metastases are shown; in these pts, CNS disease was tracked by MRI every 8 weeks Last scan date: 28 Feb 2017 ALK+ NSCLC, anaplastic lymphoma kinase–positive non–small cell lung cancer; BRG, brigatinib; CI, confidence interval; CIR, cumulative incidence rate; CNS, central nervous system; CRZ, crizotinib; iORR, intracranial objective response rate; iPFS, intracranial progression-free survival; IRC, independent review committee; MRI, magnetic resonance imaging; NR, not reached; pts, patients

[a]180 mg qd with 7-day lead-in at 90 mg

[b]Untreated, or treated and progressed [c] From Kaplan-Meier analysis.

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1346P CNS efficacy results from the phase III ALUR study of alectinib vs chemotherapy in previously treated ALK+ NSCLC

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Background: Alectinib has shown central nervous system (CNS) activity in phase II trials of previously treated *ALK*+ NSCLC. We report CNS efficacy data from the phase III ALUR study (NCT02604342) of alectinib vs standard relapse chemotherapy (CT) in pts with *ALK*+ NSCLC who previously failed platinum-based doublet CT and crizotinib.

Methods: Pts aged ≥18 years with *ALK*+ NSCLC, previously treated with CT and crizotinib were randomised 2:1 to alectinib (600mg twice daily) or CT (pemetrexed 500mg/m^2 every three weeks [q3w] or docetaxel 75mg/m^2 q3w) until disease progression (PD), death or withdrawal. After PD, pts could crossover from CT to alectinib. Primary endpoint was progression-free survival (PFS) by investigator assessment in the intent-to-treat (ITT) population. A key secondary endpoint was CNS overall response rate (CORR) by Independent Review Committee (IRC) in pts with measurable CNS mets at baseline (BL) (mC-ITT). Other CNS outcomes were CORR in pts with measurable and non-measurable CNS mets (C-ITT); 6-month cumulative incidence rate in the ITT, and C-ITT; CNS duration of response (CDOR) and disease control rate (CDCR); and safety.

Results: In total, 107 pts were randomised (alectinib n = 72, CT n = 35; ITT) of whom 76 had BL CNS disease (alectinib n = 50, CT n = 26; C-ITT); 40 had measurable CNS mets (alectinib n = 24; CT n = 16; mC-ITT) and 36 had non-measurable CNS mets (alectinib n = 26, CT n = 10; nC-ITT). CNS efficacy endpoints are shown in the Table. The 6-month cumulative incidence rate of CNS PD was 11% (alectinib) vs 48% (CT) in the ITT, 15% vs 52% in the C-ITT and 0% vs 39% in pts without BL CNS disease. Safety and tolerability profile compared favourably for alectinib vs CT.

Conclusions: CNS-related outcomes were significantly improved with alectinib vs chemotherapy in previously treated *ALK*+ NSCLC. Alectinib reduces CNS PD and prevents the development of new CNS mets.

Clinical trial identification: NCT02604342

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

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1347P Treatment beyond disease progression: ALK inhibitors in ALK-rearranged advanced NSCLC

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Background: Treatment of patients with ALK-EML4 gene rearrangement with ALK inhibitors (ALK-I) yields high response rate (RR) and prolonged progression free survival (PFS). Defining progressive disease (PD) using RECIST has been challenging in the era of targeted and immunotherapy, as some patients are perceived to be deriving ongoing benefit despite PD by RECIST. We explore the impact of treatment beyond progression with ALK-I on patient symptoms and treatment duration.

Methods: Patients with advanced ALK-rearranged lung cancer treated at the Princess Margaret Cancer Centre between 2009 and 2017 were identified. Treatment duration was obtained from medical records, assessment of PFS by RECIST 1.1 from patient imaging, and patient self-reported symptoms and performance status (Edmonton Symptom Assessment Scale (ESAS), ECOG PS) were collected prospectively.

Results: 66 patients were identified with advanced ALK-rearranged lung cancer. The median age at diagnosis was 61 years, 49% were male, 78% presented with stage 4 disease, 47 received ALK-I therapy (median 2 lines, range 1-4). Over half (26/47, 55%) continued ALK-I treatment beyond RECIST PD. PD occurred most commonly in brain (15/47), lung and/or pleura (11/47); 17/47 received local therapy (predominantly radiation) and continued ALK-I. Data on time to RECIST PD and treatment failure are shown below. Only 34/47 patients had symptom data available at baseline, 22 with severe symptoms; 70% improved with initial ALK-I treatment. At the time of RECIST PD, most of those continuing ALK-I beyond progression had not experienced deterioration of symptoms.

Table: 1347P ALK-I Treatment Patterns

	Initial ALK-I (N = 47)	Second ALK-I (N = 26)
Median Time to RECIST PD	10.1 months (range 0.3-– NR)	4.8 months (range 0.5 – NR)
Pts continuing ALK-I beyond PD	17/47 (36%)	8/26 (30%)
Median duration of treatment beyond progression	5.0 (range 0.6 – NR)	3.9 (range 1.3-21.5)

NR- not reached.

Table: 1346P CNS efficacy endpoints

	C-ITT N = 76		mC-ITT N = 40	
	Alectinib N = 50	Chemotherapy N = 26	Alectinib N = 24	Chemotherapy N = 16
CORR, % (95% CI)	36	0	54.2	0
Difference (95% CI) P value	36% (13%–57%) p < 0.001		54% (23%–78%) p < 0.001	
CDOR, months (95% CI)	NE (6.2–NE)	0	NE (3.6–NE)	0
CDCR, %	80	26.9	79.2	31.3

NE, not evaluable

Conclusions: Treatment beyond disease progression for patients with advanced lung cancer harboring ALK rearrangement is common and is often associated with maintenance of symptom burden.

Legal entity responsible for the study: UHN, University of Toronto

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1348P Overall survival (OS) in patients (pts) with EGFR T790M-positive advanced non-small cell lung cancer (NSCLC) treated with osimertinib: Results from two phase II studies

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Background: Osimertinib is an oral, potent, CNS active, irreversible EGFR-TKI approved to treat pts with T790M-positive advanced NSCLC. Here we present updated data from a pre-planned pooled analysis of Phase II studies: AURA extension (NCT01802632), AURA2 (NCT02094261).

Methods: Pts with centrally confirmed T790M-positive (by cobas® EGFR Mutation Test) advanced NSCLC, who had progressed following EGFR-TKI treatment, received osimertinib 80 mg once daily. Other inclusion criteria were measurable disease, WHO performance status 0/1 and acceptable organ function. Pts with stable CNS metastases were eligible. The primary efficacy endpoint was objective response rate (ORR) by RECIST 1.1 per blinded independent central review (BICR). Secondary endpoints included duration of response (DoR), progression-free survival (PFS), OS and safety.

Results: As of the 1 Nov 2016 data cut-off (DCO) 411 pts had received osimertinib (129 pts as second-line and 282 pts as ≥third-line); median treatment exposure was 16.4 months (mo; range 0–29.7 mo). Pooled results (BICR) were: ORR (evaluable for response set; EFR), 66% (95% confidence interval [CI] 61, 70); median DoR (EFR), 12.3 mo (95% CI 11.1, 13.8); median PFS (full analysis set), 9.9 mo (95% CI 9.5, 12.3). At DCO, 188 pts (46%) had died, 191 pts (47%) remained in survival follow up, and 32 pts (8%) had discontinued before death. Pooled median OS was 26.8 mo (95% CI 24.2, not calculable [NC]); median OS in the second-line and ≥third-line cohorts (95% CI) was 25.8 mo (24.0, NC) and NC (22.1, NC), respectively. The 12 and 24 mo survival rates were 80% and 56%, respectively. The most common (investigator assessed) possibly causally-related adverse events (AEs) were rash (grouped term 42%, [grade ≥3, 1%]) and diarrhoea (39% [<1%]). Four pts died due to possibly causally related AEs (pneumonitis [n = 3], interstitial lung disease [n = 1]).

Conclusions: With a median treatment exposure of 16.4 mo, osimertinib resulted in a median OS of 26.8 mo. This pooled analysis represents the most mature clinical trial data for osimertinib in pts with pre-treated T790M positive advanced NSCLC, and further establishes osimertinib as standard of care in this setting.

Clinical trial identification: AURA extension (NCT01802632), AURA2 (NCT02094261)

Legal entity responsible for the study: AstraZeneca

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1349P Subsequent therapies post-afatinib among patients (pts) with EGFR mutation-positive (EGFRm+) NSCLC in LUX-Lung (LL) 3, 6 and 7

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Background: Acquired resistance after front-line treatment (tx) with 1st-/2nd-generation EGFR TKIs necessitates further therapies for pts with EGFRm+ NSCLC. We explored the outcome of subsequent therapies, including other EGFR TKIs and chemotherapy (CT) after 1st-line afatinib in the LL3, 6 and 7 randomised trials.

Methods: We retrospectively assessed subsequent therapy outcomes in pts with common EGFR mutations, who were randomised to 1st-line afatinib in the LL3/6/7 trials. Data had been prospectively collected as study follow-up information. Tx duration was assessed by descriptive medians or KM estimates. Biopsies at afatinib resistance were not required in LL3/6/7.

Results: Of the 553 pts with common EGFR mutations who received 1st-line afatinib and later discontinued it, 2nd-line therapy was given in 394 (71%) pts and consisted of platinum-based CT for 252 (46%), single agent CT for 39 (7%), 1st-generation EGFR TKI for 49 (9%) and other tx for 54 (10%) pts. Median time on 2nd-line tx was 2.9 months for platinum-based and 1.4 months for single-agent CT, with no relevant difference between Del19 and L858R mutation subgroups. Among 186 (34%) pts who received 1st-generation EGFR TKIs post-afatinib, median time on tx was 3.9 months. Of 212 pts randomised to 1st-line CT in LL3 and LL6, 117 (55%) received 1st-generation EGFR TKI monotherapy as 2nd-line tx, with a median time on tx of 11.2 months. Interestingly, 34 pts received osimertinib after 1st-line afatinib, the majority in ≥ 3rd line; median time on osimertinib tx was 31.5 months (95% CI 16.8–31.5 months). Median OS for osimertinib-treated pts is not yet evaluable.

Conclusions: The majority (71%) of pts who received 1st-line afatinib were fit enough to receive subsequent therapies and there was no relevant difference in 2nd-line tx duration by Del19/L858R EGFR mutation subgroup. Introduction of a different TKI was common, with good outcome. Time on tx with osimertinib after afatinib was unexpectedly long among 34 pts; this should be examined in a larger cohort. Overall, these findings suggest that pts treated with 1st-line afatinib are well suited for subsequent therapies, including CT, 1st-generation EGFR TKIs and osimertinib.

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1350P Phase I study of TAS-121, a novel third-generation epidermal growth factor receptor (EGFR) inhibitor, in patients with EGFR mutation-positive non-small-cell lung cancer (NSCLC)

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Background: TAS-121 is an orally available, potent, novel epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI) selectively targeting EGFR activating and T790M resistance mutations. This first-in-human phase I study evaluated the maximum tolerated dose (MTD), safety, tolerability, pharmacokinetics (PK), and antitumor activity of TAS-121.

Methods: The study was conducted in Japan and consisted of three phases: dose escalation phase (DEP), expansion phase first stage (EP1), and second stage (EP2). Patients were eligible for inclusion in the study if they had advanced EGFR mutation-positive non-small-cell lung cancer (NSCLC) and were previously treated with a first or second-generation EGFR-TKI, or both. The central confirmation of EGFR T790M mutation in plasma circulating cell-free DNA or tumor tissue or both was required for enrollment in the EP2 phase.

Results: As of January 31, 2017, 127 patients had received 4–16 mg TAS-121 dose once daily (QD) or 8–12 mg daily in two divided doses (BID). The most common adverse drug reactions (ADRs) were platelet count decreased (66.9%), pyrexia (44.9%), and rash (37.8%). Other notable ADRs were interstitial lung disease (ILD) (7.9%) and pulmonary embolism (7.1%). All ILD incidences were manageable, and no treatment-related deaths occurred during the study. Dose-limiting toxicities (DLTs) were observed in five and three patients treated QD (drug-induced liver injury, platelet count decreased, urticaria, and ILD) and BID (ILD, platelet count decreased, and left ventricular failure), respectively. The MTD was determined as 10 mg QD and 8 mg BID. PK analyses showed that the area under the curve (AUC) of TAS-121 even at the lowest dose was significantly higher than that of the effective dose in preclinical tumor xenografts model. Furthermore, in the EP2 group, confirmed objective responses according to the independent central review were observed in 25.0 and 44.4% of patients (4/16 and 8/18) administered 8 mg QD and BID, respectively.

Conclusions: TAS-121 was well tolerated up to the MTD and demonstrated antitumor activity in this preliminary phase I study in patients with EGFR T790M mutation-positive NSCLC.

Clinical trial identification: JapicCTI-142651

Legal entity responsible for the study: Taiho Pharmaceutical Co., Ltd

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1351P The addition of apatinib to gefitinib or icotinib for advanced non-small cell lung cancer with acquired resistance to first-generation epidermal growth factor receptor tyrosine kinase inhibitor: An assessment of effectiveness and safety

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Background: Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) have been proved as an effective treatment of advanced non-small-cell lung cancer patients with EGFR mutations. However, resistance to EGFR-TKIs develops in most patients and leads to eventual loss of efficacy. Nowadays combined therapy inhibiting EGFR and vascular endothelial growth factor (VEGF) pathways has become a promising therapy in the treatment of advanced non-small-cell lung cancer. This study aims to assess the efficacy and safety of the addition of low dose of apatinib, a kind of TKIs targeting vascular endothelial growth factor receptor 2 (VEGFR-2), to first-generation EGFR-TKIs for advanced non-small cell lung cancer with acquired resistance to first-generation EGFR-TKIs.

Methods: We retrospectively assessed the efficacy and safety of patients with non-small cell lung cancer who had gradual progression after experiencing effective targeted therapy with first-generation EGFR-TKIs. Patients received apatinib 250 mg once daily and gefitinib 250mg once daily or icotinib 125mg thrice daily until disease progression again or unacceptable toxicity occurs.

Results: The study group comprised 33 Chinese patients, among whom 15 (45.5%) were males and 20 (60.6%) were non-smokers. The median duration of combined therapy was 5.5 month. 17 patients (51.5%) had a partial response (PR) and 13 patients had stable disease (SD). The overall response rate was 51.5%. 21 cases of adverse events were observed in this study. The incidence of severe adverse events was only 3.0%. The incidence of adverse events in patients decreased in hypertension, rash, proteinuria, hand-foot syndrome, gastrointestinal reaction, mucosal inflammation, bleeding, alanine aminotransferase increased and hypoovarianism.

Conclusions: The addition of low dose of apatinib to gefitinib or icotinib can significantly inhibit tumor growth and improve the progression-free survival of patients received first-generation EGFR-TKIs. Potential advantage in safety were identified which warrant further validation.

Legal entity responsible for the study: None

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1352P Leptomeningeal carcinomatosis from EGFR-mutated non-small cell lung cancer

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[1]Neurological Surgery, Chiba Cancer Center Hospital, Chiba, Japan, [2]Respirology, Chiba Cancer Center, Chiba, JapanBackground: Diagnosis of leptomeningeal carcinomatosis (LMC) is made based upon the findings on MRI (LMCi), and/or cytologically confirmed cancer cells in the cerebrospinal fluid (CSF) (LMCc). However, in EGFR-mutated (EGFRm) cases, brain metastasis (BM) has a tendency to arise close to CSF space, and discrepancies between imaging and cytological results makes it difficult to construct treatment strategy. Although the effect of tyrosine kinase inhibitors (TKIs) on LMC has been expected, a little is known regarding the effect and limitation of TKIsMethods: Overall survival (OS) after diagnosis of BM were compared between patients with and without LMC at diagnosis, and prognostic value of LMCi and LMCc were retrospectively compared to clarify the reliable diagnostic method of LMC. Survival differences of patients with LMC after treatment with and without TKIs were also compared to evaluate the efficacy of TKIs on LMC

Results: From Aug. 2006 to now, 215 BMs from *EGFR*m non-small cell cancers were treated. At diagnosis of BMs, LMCi was diagnosed in 140 cases. Among these cases, CSF cytology was evaluated in 113 cases, but malignant cells were detected only in 47 cases (41.6%). TKIs were administrated in 159 patients. Without TKIs, OS after BM with LMCi (9.5m) was shorter than that without LMCi (26.9m) (HR: 1.75, P=0.096), but this difference was reduced in patients treated with TKIs (18.1m vs. 20.9m, P=0.123).

On the other hand, without TKIs, OS after BM with LMCc (4.9m) was extremely worse than that without LMCc (16.6m) (HR:7.76, *P*=0.001), but this significant difference was lost by TKIs (HR:1.16, *P*=0.671). During the follow up, 152 deaths were observed, and 45 were owing to the progression of intracranial lesions (CNS death). Not LMCi but LMCc was a significant risk factor of CNS death (OR: 0.59 and 6.26, *P*=0.148 and 0.002, respectively). TKI had decreased the incidence of CNS death from 100% to 64% in LMCc cases, but LMCc was still a significant risk factor of CNS death even with TKIs (OR: 5.13, *P*=0.017), and disappearance of cancer cells in CSF by TKIs was observed only in 41.2% of patients.

Conclusions: MRI was insufficient to diagnose LMC. TKIs were strongly recommended for patients with LMCc, but its' effect was still inadequate in half of the patients.

Legal entity responsible for the study: Chiba Cancer Center

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1353P CNS response to osimertinib in Asian-Pacific patients (pts) with T790M-positive advanced NSCLC: data from an open-label Phase II trial (AURA17)

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Background: Osimertinib has shown CNS efficacy in a pooled analysis of two Phase II trials (AURA extension: NCT01802632, AURA2: NCT02094261) in pts with T790M-positive advanced NSCLC. We report osimertinib efficacy in CNS metastases (mets) from a Phase II, open-label, single-arm trial (AURA17: NCT02442349) in Asia-Pacific pts with T790M-positive advanced NSCLC who had progressed on prior EGFR-TKI therapy, with or without additional anti-cancer regimens.

Methods: Pts with stable, asymptomatic, CNS mets were eligible for enrolment and received osimertinib 80 mg once daily. This prespecified subgroup analysis was conducted in pts with CNS mets present on baseline brain scan as assessed by blinded independent central neuroradiology review (BICR). Endpoints included CNS objective response rate (ORR), duration of response (DoR) and progression-free survival (PFS) by RECIST 1.1. The CNS full analysis set (cFAS) comprised pts with ≥1 measurable and/or non-measurable CNS lesion present on baseline brain scan by BICR; the CNS evaluable for response set (cEFR) comprised pts with ≥1 measurable CNS lesion.

Results: At the data cut-off of 4 November 2016, 59/171 pts (35%) were included in the cFAS. In the cFAS and cEFR (n = 23), 3 and 0 pts had brain radiotherapy ≤6 months prior to study entry, respectively. CNS ORR was 42% (25/59; 95% CI 30, 56) for the cFAS and 70% (16/23; 95% CI 47, 87) for the cEFR. Median CNS DoR was not reached (95% CI 9.2, not calculable [NC]) for the cFAS and 11.1 months (95% CI 8.2, NC) for the cEFR. CNS DCR was 85% (95% CI 73, 93) for the cFAS and 91% (95% CI 72, 99) for the cEFR. Median CNS PFS was not reached in both cFAS (95% CI 12.4, NC) and cEFR groups (95% CI 9.4, NC), with a median follow-up for CNS PFS of 7.1 and 8.2 months, respectively. At 12 months, 70% (95% CI 53, 82) of pts in the cFAS and 61% (95% CI 31, 81) of pts in the cEFR were estimated to remain on study, alive and CNS progression-free.

Conclusions: These data are consistent with previous reports of CNS response to osimertinib in pts with T790M-positive advanced NSCLC in global studies, and demonstrate clinically meaningful efficacy in Asian-Pacific pts with CNS mets.

Clinical trial identification: NCT02442349

Legal entity responsible for the study: AstraZeneca

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Disclosure: C. Zhou: Lecture honorarium: Eli Lily, AZ, Roche, Pfizer, Sanofi, BI, Henrui Advisory board: Roche, BI, AZ. Y. Lu: Consulting or Advisory Role: AstraZeneca, Hoffmann-La Roche, Eli Lilly, Pfizer, Elekta, Varian Medical Systems. J. Wang, Y. Chen: Employee of AstraZeneca. Y-L. Wu: Speaker fees from AstraZeneca, Roche, Eli Lilly, Sanofi, Pfizer. All other authors have declared no conflicts of interest.

1354P Osimertinib in Asia-Pacific patients (pts) with EGFR T790M-positive advanced NSCLC: Updated Phase II study results including progression-free survival (PFS)

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Background: Osimertinib is an oral, potent, CNS active, irreversible EGFR-TKI selective for EGFR-TKI sensitising and T790M resistance mutations. AURA17 (NCT02442349) is a Phase II, open-label, single arm study investigating the safety and efficacy of osimertinib in Asia-Pacific pts with T790M-positive advanced NSCLC, who had progressed on prior EGFR-TKI therapy, with or without additional anti-cancer regimens.

Methods: Eligible pts had measureable disease, WHO performance status 0/1 and acceptable organ function; asymptomatic CNS metastases were allowed. T790M-positive status was confirmed by central testing of biopsy samples using the cobas® EGFR Mutation Test. Osimertinib 80 mg was administered orally once daily until disease progression. The primary endpoint was objective response rate (ORR) according to RECIST 1.1 by blinded independent central review. Secondary endpoints included duration of response (DoR), PFS, disease control rate (DCR), overall survival, safety and tolerability.

Results: As of 4 Nov 2016 data cut-off (DCO), 171 pts had received osimertinib (53 [31%] second-line; 118 [69%] ≥third-line), median treatment exposure was 12.3 (range 0.2–14.6) mo. Median age 60 (range 26–82) years; female 68%; Chinese ethnicity 87%; never smokers 78%; EGFR Exon 19 deletion 64%; EGFR L858R mutation 35%; CNS metastases at study entry 37%. Confirmed ORR in pts evaluable for response (n = 166) was 63% (95% confidence interval [CI] 55, 70) and DCR was 89% (95% CI 83, 93). Median DoR was 9.9 mo (95% CI 8.3, not calculable). Median PFS in the full analysis set (n = 171) was 9.7 mo (95% CI 7.0, 11.1); 94 pts (55%) had progression. At DCO, 39 pts had died (23%). All causality adverse events (AEs) of CTCAE Grade ≥3 were reported by 43 (25%) pts. Most common AEs were diarrhoea 35% (Grade ≥3 1%) and rash grouped term 27% (Grade ≥3 0%). There was one reported case of interstitial lung disease and pneumonitis, respectively.

Conclusions: The high ORR of 63% was supported by the durable response assessed by DoR (median 9.9 mo) and PFS (median 9.7 mo). The efficacy data were consistent with global clinical trials of osimertinib. No new safety signals were observed.

Clinical trial identification: NCT02442349

Legal entity responsible for the study: AstraZeneca

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1355P Activity of afatinib in heavily pretreated patients (pts) with HER2 mutation-positive (HER2m+) advanced non-small cell lung cancer (NSCLC): findings from a global named patient use (NPU) program

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Background: Approximately 1–4% of lung adenocarcinomas harbour a *HER2* mutation. No targeted treatment is approved yet for this NSCLC pt subgroup. Initial results for the treatment of *HER2*m+ NSCLC with the irreversible ErbB family blocker, afatinib, have been encouraging, with some pts showing notable responses or promising disease control. Pts with *HER2*m+ NSCLC were included in a global NPU program for afatinib, which was initiated in 2010, and their treatment outcomes are presented here.

Methods: A global NPU program included patients with advanced NSCLC who had progressed after clinical benefit on prior erlotinib/gefitinib, had an activating *EGFR* or *HER2* mutation, had exhausted all other treatment options; and were ineligible for afatinib trials. Pts received daily oral afatinib (starting dose: 40 or 50 mg). Collection of safety data was mandatory. Time to treatment failure (TTF) was defined as time from start of afatinib treatment to the date of treatment discontinuation.

Results: As of May 2017, data were available for 28 pts with *HER2*m+ NSCLC (male/female: 12/16 [43/57%]; median age: 55 yrs; starting dose 40/50 mg: 17/11 [61/39%]). Patients were heavily pretreated; 16 (57%) received afatinib as ≥ 4th-line treatment and 7 (25%) had received prior targeted anti-HER2 treatment. Median TTF for afatinib, calculated for all 28 patients was 2.9 months and, notably, 9 (32%) pts had TTF >1 yr. Response assessments were reported for 16 pts; disease control rate was 69% (11/16 pts) and objective response rate was 19% (3/16 pts). No new or unexpected safety findings were observed.

Conclusions: This analysis of a heavily pre-treated pt population with *HER2*m+ NSCLC from the afatinib NPU program showed a promising 32% of pts with TTF >1 yr, durable disease control and a manageable safety profile. With the limitation of retrospective analysis, and also considering that different *HER2* mutations can display different treatment sensitivities, these findings suggest that the evaluation of afatinib in earlier treatment lines in *HER2*m+ NSCLC pts may be warranted.

Legal entity responsible for the study: Boehringer Ingelheim

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1356P Octogenarians with EGFR-mutated non-small cell lung Cancer (NSCLC) treated by Tyrosine Kinase Inhibitor (TKI): A multicentric real world study assessing tolerance and efficacy. OCTOMUT study GFPC 07-15

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Background: Tyrosine kinase inhibitors (TKI) are the standard of treatment in first line for advanced EGFR-mutated NSCLC. Few data exist about their tolerance and efficacy in octogenarians particularly in Caucasian population. The purpose of this multicentric real world study was to assess tolerance and efficacy of EGFR-TKI in this population.

Methods: We retrospectively identified patients aged 80 years or older with EGFR-mutated NSCLC treated by EGFR-TKI between 01/01/2011 and 31/03/2015 whatever the line of treatment. Patients were described according to their clinical characteristics, management and outcomes (progression-free survival (PFS) and overall survival (OS).

Results: The 20 french participating centers included 114 patients: 77% were women, the median age was 83,9 ±3,9 years; 98,2% were caucasians and 84,6% were home life (45% had home help), 71% took more than 5 drugs/d. Respectively 64%,17.5% and 8,5% of patients had a performance status of 0-1/2/3 at diagnosis. 76% of them were non-smokers, 95,6% had adenocarcinomas; 80%/13%/7% had respectively stage IV/III/II–I at treatment initiation. EGFR mutations were identified on exon 19 (46,5%), exon 21 (40,3%), exon 20 (5,2%). A geriatric assessment was assessed in 35% of cases. Median time between first symptoms and diagnosis was 55 days. 97.3% of the patients were treated by TKI as first or second line. Median PFS was 11,9 months, 95% CI: 8,6-14,7. Response and disease control rates were 67% and 79% respectively. In 40% of the cases EGFR-TKI treatment was maintain beyond progression. After progression, 44,7% of the patients received another line of treatment (chemotherapy: 44,7%). Median OS was 20,9 months, 95% CI: 14,3-27,1. Main toxicities were cutaneous: 66% (grade 3/4:10%), diarrhea 56% (grade 3/4:15%, grade 5: 2%), others 25,6% (grade 3/4: 41%).

Conclusions: In this real-world analysis, compared to younger, octogenarians patients with EGFR-mutated NSCLC treated by EGFR TKI present comparable outcomes and toxicity profile. Geriatric assessment is still under-used in this population.

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Legal entity responsible for the study: Groupe Français de Pneumo Cancérologie (GFPC)

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Disclosure: R. Corre: In the last five years, has received honoraria for attending scientific meetings, speaking, organizing research or consulting from Roche, Astra-Zeneca, Boehringer-Ingelheim, Lilly, Bristol-Myers-Squibb, Novartis. H. Doubre: In the last five years, has received honoraria for attending scientific meetings, speaking, organizing research or consulting, from Astra-Zeneca, Novartis, Lilly, Boehringer-Ingelheim, Roche, Leo Pharma. C. Chouaid: In the past 5 years, has received fees for attending scientific meetings, speaking, organizing research or consulting from AZ, Boehringer Ingelheim, and Roche. J.B. Auliac: In the last five years, has received honoraria for attending scientific meetings, speaking, organizing research or consulting, from Boehringer Ingelheim, Hoffman-Roche, BMS, Lilly and Pfizer. All other authors have declared no conflicts of interest.

1357P Prospective evaluation of the relationship between erlotinib concentration and efficacy in patients with non-small cell lung cancer harboring EGFR-activating mutations

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Background: Erlotinib is an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI), which has shown improved clinical outcomes in the treatment of patients with non-small cell lung cancer (NSCLC) harboring EGFR exon 19 deletions and exon 21 L858R mutations. Previous reports regarding the relationship between erlotinib pharmacokinetics and pharmacodynamics evaluated toxicities but not efficacy. Therefore, to evaluate the relationship between erlotinib exposure and efficacy, we conducted this prospective study.

Methods: Erlotinib was orally administered at a dose of 150 mg/body once daily to patients with NSCLC, who were not previously treated with EGFR-TKIs. A series of blood samples were taken at predetermined times on day 1 to calculate the area under the concentration-time curve (AUC). Erlotinib trough concentrartions (C_{trough}) at each visit and the level of alpha1-acid glycoprotein (AAG), which is a binding protein of erlotinib in serum, were measured.

Results: Of 70 patients enrolled, 61 had activating EGFR mutations (30 patients with exon 19 deletions and 31 with exon 21 L858R mutations). The AUC was 37.0 μg·h/mL in median (range; 9.7-63.3). Objective response rate and median progression-free survival (PFS) were 72% and 12.4 months in the patients with EGFR-activating mutations. Response was not associated with AUC. There was also no significant difference in PFS between patients with AUC > 37.0 μg·h/mL and ≤ 37.0 μg·h/mL. C_{trough} was significantly correlated with the grade of skin rash ($p < 0.01$), but not with objective response. In multivariate analyses, pretreatment AAG level, which was 0.97 g/L in median (0.53-3.83), was found to be a significant factor in PFS for patients with EGFR-activating mutations (median PFS; AAG > 0.97 g/L, 7.9 months; AAG ≤ 0.97 g/L, 16.8 months, $p < 0.01$).

Conclusions: The lack of a relationship between erlotinib exposure and efficacy shows that the approved dose of erlotinib is sufficient to reach the therapeutic range in EGFR-activating mutant NSCLC, even with dose reduction due to toxicities. AAG level can be a prognostic factor for patients with NSCLC harboring EGFR-activating mutations treated with erlotinib.

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Legal entity responsible for the study: Shizuoka Cancer Center

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1358P First-in-human phase I study of PF-06747775, a third-generation mutant selective EGFR tyrosine kinase inhibitor (TKI) in metastatic EGFR mutant NSCLC after progression on a first-line EGFR TKI

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Background: PF-06747775 ("PF-7775") is a selective, 3rd generation Epidermal Growth Factor Receptor (EGFR) TKI effective against EGFR sensitizing and T790M mutations in preclinical models. Enrollment was completed in a phase I study of PF-7775 in EGFR mutant (EGFRm+) NSCLC patients (pts) who progressed after a prior EGFR TKI.

Methods: EGFRm+ NSCLC pts with resistance to first-line EGFR-TKIs enrolled in a multicenter trial in 6 dose escalation (25 mg–600 mg) and 2 dose expansion cohorts

(200 mg and 300 mg). Biopsy for EGFR T790M at clinical progression was not required for study entry. PF-7775 was given orally once daily. All pts were assessed for response, adverse events (AEs), and pharmacokinetics. Plasma T790M testing was conducted retrospectively.

Results: As of a 3 Feb17 data cutoff, 44 pts were enrolled (59% female, median age 63.5, Asian/Caucasian 73/25%).The most common all grade AEs in all enrolled patients ($\geq$ 25%) were: diarrhea (57%), rash (59%), paronychia (52%), dermatitis acneiform (34%), stomatitis (32%), pruritus (27%), dry skin (25%), and rhinorrhea (25%). Grade 3 events were consistent with known EGFR TKI toxicities (diarrhea and skin toxicity) and easily managed. No grade 4 treatment related AEs were noted in dose escalation or expansion. Nineteen pts (43%) had dose reductions due to treatment related AEs at the higher dose cohorts and the RP2D of 200 mg was selected based on the AE profile and tolerability of drug at this dose for longer term administration. The prevalence rate of T790M, L858R, and del 19 in plasma samples, along with data correlating ORR (CR and PR rate) and CBR (CR + PR + SD) is ongoing.

Conclusions: PF-7775 is well tolerated at 200 mg dose in EGFRm+ NSCLC pts with acquired resistance to first-line EGFR-TKIs. Data relating mutational status to response rate in plasma is ongoing.

Clinical trial identification: NCT02349633

Legal entity responsible for the study: Pfizer Inc.

Funding: Pfizer Inc.

Disclosure: P. Senico, W. Ma, J. Masters, N. Pathan, Z. Goldberg: Employee of Pfizer and declare Pfizer stock ownership. B.C. Cho: Conducting Pfizer corporate-sponsored research. All other authors have declared no conflicts of interest.

1359P Impact on OS and PFS of 2nd and 3rd generation TKI in EGFR mt+ and ALK+ pts: Results of the NOWEL network

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Background: Clinical research data shows that early mutation testing for pts with NSCLC stage IV could lead to an effective choice of therapy for pts with proven mutations. Targeted therapies achieve a higher ORR, OS, PFS and a better quality of life than chemotherapy in mt+ pts. With the advent of 2nd and 3rd generation TKÍs effective in 1st generation TKI resistant tumors, we wanted to study the impact of these drugs on the outcome of pts in a real life setting.

Methods: 1381 pts from three cancer centers diagnosed with non-squamous cell NSCLC stage IV (UICC 7) were examined. Methods for the mutation testing was performed according to the German Oncopedia guidelines using either Sanger Sequencing or COBAS® or Next Generation Sequencing (hybrid capture NGS, New Oncology Cologne).

Results: 879/1381 (64%) consecutive pts with non-squamous cell NSCLC from three cancer centers were studied for the presence of tumor mutations, especially for EGFR and ALK mt+. The EGFR mt+ rate was 16.6% (141/847), and the ALK-translocation rate 3.8% (24/635). Median OS in EGFR mt+ pts was 28 (n = 79) vs. 28 (n = 38) vs. 16 (n = 14) months respectively (center 1 vs. center 2 vs. center 3). Median OS in ALK mt+ pts was 24 months (n = 17) in center 1 and 11 months (n = 5) in center 2 ($p < 0.033$). The ORR in the CR/PR group was 54.2% for pts treated with chemotherapy and 77% for pts treated with TKI on 1st line therapy. The chance to reach a CR/PR on 1st line therapy is 2.83 higher for pts on TKI than for pts on chemotherapy ($p < 0.02$). The use of 3rd generation TKI Osimertinib (n = 19) lead to a significantly higher OS (n = 19, median OS 67 months) than the use of only 1st and 2nd generation TKI (n = 111, median OS 23 months, $p < 0.000$). Pts treated with 3rd gen TKI had significantly longer PFS (11 months, n = 7) than patients treated without 3rd generation TKI (5 months, n = 45) ($p < 0.037$). Similarly, use of 2nd and 3rd generation ALKi impacted significantly on median OS: Crizotinib alone (n = 8), 17 months, Crizotinib followed by Ceritinib and/or Brigatinib (n = 10) median OS not reached and 3 months for other therapies (n = 6) ($p < 0.001$).

Conclusions: Small differences in OS were observed, depending on the treatment centers, but the use of multiple EGFR and ALK-I impacted highly significantly on the outcome of pts with EGFR and ALK mt+ in a real life setting.

Legal entity responsible for the study: Faculty 6 University of Oldenburg

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1360P Phase II trial of AZD9291 in second line treatment after acquired resistance with T790M mutation detected from circulating tumor DNA (LiquidLung-O-Cohort 2)

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Background: Administering the best treatment after acquiring resistance to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) requires the knowledge of the resistance status. In this trial, the treatment efficacy of osimertinib (AZD9291) was assessed in patients with non-small-cell lung carcinoma (NSCLC) harboring T790M resistance mutation, which was detected in the circulating tumor DNA (CtDNA) without re-biopsy of the tumor tissue.

Methods: To prove 60% response rate of osimertinib compared to 30% as null hypothesis, and considering 10% drop out rate, 19 subjects was recruited. To extract CtDNA, 15 mL of peripheral blood was withdrawn and centrifuged immediately before storage. Cobas® v2 RUO (Roche diagnostics) and PANA mutyper® (Pangene, Korea) were used to detect the EGFR mutations from CtDNA. Osimertinib was prescribed as an 80mg tablet once in a day irrespective of the food intake.

Results: Eighty patients with acquired resistance to prior EGFR TKIs were screened for T790M resistance mutation, and the CtDNA of 21 subjects (26.3%) showed T790M mutation. T790M mutation was detected by both PANA mutyper® and Cobas® in 13 cases, T790M was detected only by PANA mutyper® in 4 cases, and only by Cobas® in 4 cases. Nineteen subjects (age: 64.4 $\pm$ 11.6 years old, 14 women, 5 men) were enrolled in this prospective single arm trial from September 2016 to April 2017. Prior EGFR TKIs were afatinib (n = 3), erlotinib (n = 4), gefitinib (n = 10), erlotinib and afatinib (n = 1), and gefitinib and afatinib (n = 1). Twelve subjects had exon 19 deletion of EGFR gene, 4 had L858R point mutation, one showed exon 19 deletion and L858R, 1 had G719X, and 1 case showed no activating mutation.

Conclusions: By April 2017, the response to osimertinib was evaluated in 13 subjects; 4 subjects dropped out from this trial before response evaluation, and the responses in 2 subjects are still pending for evaluation. Among the 13 subjects whose responses were evaluated (efficacy analysis set), partial remission was observed in 8 cases (61.5%). In the final efficacy analysis, toxicity and survival analyses will be performed.

Clinical trial identification: NCT02769286

Legal entity responsible for the study: Young-Chul Kim

Funding: AstraZeneca

Disclosure: Y-C. Kim: This study was funded by AstraZeneca. All other authors have declared no conflicts of interest.

1362P Safety and clinical activity of DS-6051b, a ROS1/NTRK inhibitor, in Japanese patients with NSCLC harboring ROS1 fusion gene

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Background: ROS1 or NTRK genetic abnormality is a key oncogenic driver, especially in non-small cell lung cancer (NSCLC). DS-6051b is an orally available and potent selective small molecule inhibitor of ROS1 and NTRK. Preclinical pharmacology studies exhibited antitumor activity of DS-6051b against several types of tumor with ROS1 or NTRK fusion gene.

Methods: This is an ongoing phase 1 study in Japanese patients with advanced solid tumors harboring either a ROS1 or NTRK fusion gene. Patients receive continuous once daily (QD) dosing of DS-6051b. Pharmacokinetics (PK) samples are collected from Day1 to Day22. If patients consented, liquid biopsy samples for circulating tumor DNA (ctDNA) analysis are collected at screening and study discontinuation. The primary objective is to evaluate the safety profile and secondary objectives are to determine the maximum tolerated dose (MTD), the recommended phase 2 dose (RP2D) and to assess the PK profile. Exploratory objectives are to assess the tumor responses to DS-6051b by means of Investigator evaluation per RECIST v.1.1 and to explore biomarkers. ClinicalTrials.gov identifier: NCT02675491.

Results: As of Apr 10, 2017, 15 patients are enrolled. The median age is 51 (34-69) years, 46.7% are female, all 15 patients are ROS1 fusion positive NSCLC, and 4 had prior crizotinib (CRZ) treatment. Patients received DS-6051b at doses of 400mg QD (n = 6), 800mg QD (n = 3) and 600mg QD (n = 6). Common adverse events are AST increased, ALT increased, diarrhea and nausea. There are no DLTs in the 400mg and 600mg QD cohorts, and 2 out of 3 patients in the 800mg QD cohort experienced DLTs with grade 3 ALT increased. In 12 patients who had measurable target lesions, 7 demonstrated partial response (PR) and 5 demonstrated stable disease. In 9 CRZ-naïve patients, the overall response rate is 66.7% (6 PRs) and the disease control rate is 100%. Early clinical response was also shown in a subject with brain metastasis. The plasma drug concentration increased in a dose-dependent manner. Currently, ctDNA analyses obtained from pre/post DS-6051b treatment are ongoing.

Conclusions: DS-6051b is well tolerated in Japanese patients with NSCLC and effective especially in CRZ-naïve. The MTD/RP2D is identified as 600mg QD.

Legal entity responsible for the study: Daiichi Sankyo Co., Ltd.

Funding: None

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1363P Efficacy and safety of abemaciclib combined with either LY3023414 or pembrolizumab in stage IV NSCLC

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Background: Abemaciclib (abema), a cyclin D kinase 4 & 6 inhibitor, has single-agent activity and an acceptable safety profile when dosed continuously in patients with previously treated metastatic NSCLC (NCT01394016). In tumor models, CDK inhibition induces an escape pathway involving PI3kinase (PI3K) and abema induces synergistic immune activation with checkpoint inhibitors. We report on activity and safety of abema plus LY3023414 (LY), a PI3K/mTOR dual inhibitor, and abema plus pembrolizumab (pembro), an anti-PD-1 antibody, in an ongoing Phase 1b open-label, 3 + 3 multicenter trial of previously treated advanced NSCLC (NCT02079636).

Methods: For escalation, Abema [100, 150 mg, or 200 mg (cohort D only)] was given orally on a continuous schedule every 12 hours (q12h) with LY at 100, 150, or 200 mg q12h (cohort D) or with pembro at 200 mg I.V. infusion q3 weeks (cohort E). Confirmatory cohorts were given 150 mg abema with 150 mg LY or 200 mg pembro. Pts were treated until progression or other discontinuation criteria were met. Responses were evaluated with RECIST v1.1. Safety assessments followed the NCI-CTCAE v4.0.

Results: As of 01-Mar-2017, cohort D (n = 29) had 62.1% males, 37.9% ≥65 years of age, median # prior systemic therapies=3; 86.2% stage IV; 72.4% adenocarcinoma; 62.1% ECOG PS = 1. 9 pts (31%) had stable disease (SD), 3 pts had progressive disease (PD), and the status for the remaining 17 pts was unknown or under evaluation. There were 3 deaths unrelated to study drug (2 disease related and 1 stroke). 24/29 pts had a treatment emergent, related AE (TRAE), 10/24 had a Grade 3/4 TRAE. Any grade TRAEs (>30% pts) were nausea (51.7%), diarrhea (51.7%), vomiting (41.4%), and decreased appetite (31%). Cohort E had 19 pts entered (42.1% male, 42.1% ≥65 years of age, median # prior systemic therapies=2; 52.6% stage IV; 89.5% adenocarcinoma; 57.9% ECOG PS = 1). 8 pts (42.1%) had SD, 1 had PD, and the status for the remaining 10 pts was unknown or under evaluation. There were 3 disease related deaths. 15/19 pts had a TRAE, 5/15 had a G3/4 TRAE. Any grade TRAEs (>30% pts) were fatigue (n = 47.4%) and diarrhea (36.8%).

Conclusions: To date, stable disease as best response and acceptable safety have been observed using combinations of abema and either LY or pembro in advanced NSCLC.

Clinical trial identification: NCT02079636

Legal entity responsible for the study: Eli Lilly and Company

Funding: Eli Lilly and Company

Disclosure: P. Garrido Lopez: Advisor/Board member: MSD, Pfizer, BMS, Novartis, Roche, BI, Guardant Speakers Bureau: MSD, Pfizer, BMS, Novartis, Roche Honorarium recipient: BI J. Goldman: Research grant from Eli Lilly and company Eli Lilly and Company's Scientific Advisory Board member. K. Kelly: Attended a Lilly advisory board in Feb 2017 that discussed Abemaciclib. E.S. Kim: Celgene - Consultant Boehringer Ingelheim - Consultant Eli Lilly - Consultant AstraZeneca – Consultant. Z. Yang, L. Amstutz, W.J. John: Full time employee of Eli Lilly and Company. K-J. Ingram: Stock ownership in Eli Lilly and Company. Employee of Eli Lilly and company. M. Provencio Pulla: Corporate-sponsored research (investigator): GI Therapeutics, Eli Lilly and Company. All other authors have declared no conflicts of interest.

1364P Final clinical results from SUNRISE: A phase III, randomized, double-blind, placebo-controlled multicenter trial of bavituximab plus docetaxel in patients with previously treated stage IIIb/IV nonsquamous non-small cell lung cancer

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Background: Exposed phosphatidylserine (PS) in the tumor microenvironment is highly immunosuppressive. Bavituximab targets PS and repolarizes M2 macrophages to M1 resulting in production of pro-inflammatory cytokines such as IFN-γ and IL-12, maturation of dendritic cells, and tumor specific cytotoxic T lymphocyte immunity. In a prior blinded Phase II trial in 2nd-line nonsquamous NSCLC, bavituximab + docetaxel was well-tolerated and demonstrated 60% improvement (11.7 vs 7.3 months) in median overall survival (mOS) (HR, 0.66; P = 0.11) compared to control.

Methods: 597 patients with Stage IIIb/IV nonsquamous NSCLC that progressed on platinum-doublet chemotherapy were randomized 1:1 to receive up to six 21-day cycles of docetaxel in combination with weekly 3 mg/kg bavituximab (B+D) or placebo (D) until progression or toxicity. The primary endpoint was OS. Secondary endpoints included progression-free survival (PFS), objective response rate (ORR) and safety.

Results: With 12 months follow-up from the last patient randomized and ~85% of the targeted OS events reached, mOS was 10.5 months (95% confidence interval [CI], 8.4-11.9) among 297 patients in B+D and 10.9 months (95% CI, 9.2-12.1) among 300 patients in D (HR, 1.06; P = 0.533). PFS was 4.2 months (95% CI, 3.9-4.6) in B+D and 4.1 months (95% CI, 3.2-4.8) in D (HR, 1.02; P = 0.876). The ORR was 15% in B+D vs. 11% in D (odds ratio, 0.7; P = 0.15). The safety profile was similar between groups. Grade 3 or higher adverse events occurred in 68% of patients in B+D and 60% in D. In an exploratory analysis of OS for patients who received subsequent immune checkpoint inhibitors (ICI), the mOS was not reached (95% CI, 15.2-NA) in B+D (n = 46) and 12.6 months (95% CI, 10.4-17.8) in D (n = 47) (HR, 0.46; P = 0.006).

Conclusions: The combination of B+D was well-tolerated though no OS difference was observed compared to D alone in the ITT population of previously treated nonsquamous NSCLC. An exploratory analysis of patients who received subsequent ICI found significantly longer OS in patients who received prior B+D than those who received D and support further clinical investigation of B+ICI in NSCLC.

Clinical trial identification: NIH = NCT01999673 EudraCT = 2013-003953-13

Legal entity responsible for the study: Peregrine Pharmaceuticals Inc.

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Disclosure: P. Bidoli: Eli Lilly personal fees and advisory board BMS personal fees and advisory board Boehringer personal fees and advisory board. M. Reck: Honoraria for lectures and consultancy with Hoffmann-La Roche, Lilly, MSD, Merck, BMS, AstraZeneca, Celgene, Boehringer-Ingelheim, Pfizer, Novartis. N. Kallinteris, J. Lai: Peregrine Pharmaceuticals Inc. = employee, stock ownership M. Tang: Peregrine = Employee, stock owner. J. Shan: Employee, officer and stock owner for Peregrine Pharmaceuticals Inc. All other authors have declared no conflicts of interest.

1365P Effect on quality of life (QOL) of adding cisplatin to single-agent first-line chemotherapy in elderly patients with advanced non-small cell lung cancer (NSCLC): A joint analysis of the multicentre, randomized, phase 3 MILES-3 and MILES-4 studies

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Background: The effect on QOL of adding platinum to first line treatment of elderly patients (pts) with advanced NSCLC is unknown. In this setting, MILES-3 and MILES-4 trials prospectively showed that adding cisplatin (Cis) to single-agent gemcitabine (Gem) or pemetrexed (Pem) does not significantly prolong overall survival.

Methods: Advanced NSCLC pts, >70 years old, ECOG performance status 0-1, were eligible. In MILES-3, pts with any tumor histology were randomly assigned to CisGem or Gem. In MILES-4, pts with non-squamous histology were randomly assigned to CisGem, Gem, CisPem or Pem. The trials were joined together because of slow accrual. Overall survival was the primary endpoint. QOL (EORTC QLQ C30 and LC13) was a secondary endpoint. Five questionnaires were planned in MILES-3 and 7 in MILES-4; QOL was measured in both the trials at 3 time points (baseline, end cycle 1, end cycle 2) used for joint analysis. Intention-to-treat strategy was applied; analyses were adjusted for baseline QOL, stage, PS, gender, age, size of centre, trial, histotype and companion drug.

Results: Overall, 458/531 pts (86.3%) answered baseline questionnaire. Rate of missing questionnaires at end cycle 1 and 2 was slightly higher among pts receiving Cis. Mean change in fatigue after cycle 1 ($P = 0.01$) and in sore mouth after cycle 2 ($P = 0.02$) were worse with Cis. Using a 10% change from baseline as clinically relevant threshold to categorize response, alopecia was significantly worse with Cis ($P = 0.05$). In time to deterioration analysis with progression/death as competitive risk, sore mouth and alopecia deteriorated more with Cis (HR 1.72 95%CI 1.02-2.89 $P = 0.04$ and HR 1.84 95%CI 1.09-3.10, $P = 0.02$, respectively). Response analysis in MILES-3 confirmed findings of the joint analysis while time to deterioration analysis in MILES-4 did not find any significant difference. Cis did not significantly improve any QOL item, in any type of analysis.

Conclusions: The addition of Cisplatin did not improve QOL of elderly patients with advanced NSCLC. Partially supported by AIFA (grant FARM8KAJZK) and Eli Lilly.

Clinical trial identification: MILES 3 EudraCT number: 2009 − 013540−36 MILES 4 EudraCT number: 2012-000164-25

Legal entity responsible for the study: Istituto Nazionale Tumori, IRCCS, Fondazione G. Pascale

Funding: Eli Lilly

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1366P Effect of nab-paclitaxel/carboplatin (nab-P/C) induction therapy on quality of life (QoL) of patients with squamous (SCC) non-small cell lung cancer (NSCLC) (ABOUND.sqm)

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Background: Patients with advanced NSCLC experience a high symptom burden; therefore, identifying a treatment that maintains or improves QoL is important. QoL outcomes in patients with SCC NSCLC receiving nab-P/C in the induction part of the ABOUND.sqm study are reported.

Methods: Patients with stage IIIB/IV SCC NSCLC and no prior chemotherapy for metastatic disease received 4 cycles of induction therapy with nab-P 100 mg/m^2 days 1, 8, and 15 + C area under the curve 6 on day 1 (21-day cycles). Patients not progressing after induction received (2:1) maintenance nab-P 100 mg/m^2 days 1 and 8 (21-day cycles) + best supportive care (BSC) or BSC alone until progression/unacceptable toxicity. The primary endpoint is progression-free survival (randomization to maintenance). Patient-reported QoL (exploratory endpoint) was assessed on day 1 of each cycle using the Lung Cancer Symptom Scale (LCSS) and EuroQoL 5 Dimensions-5 Levels (EQ-5D-5L).

Results: In 343 patients receiving treatment in the induction phase were evaluated. Median age was 68 years; 90% were white, 68% male, and 67% had ECOG PS 1. Of 332 patients treated for $\geq$ 2 cycles, 298 (90%) completed baseline + $\geq$ 1 postbaseline QoL assessment. During induction, the mean change from baseline in LCSS symptom burden index and total score ranged from 5.5%-7.8% and 5.5%-7.7%, respectively. Clinically meaningful improvements ($\geq$ 10 mm [visual analog scale]) from baseline were observed in composite LCSS pulmonary symptom items of cough, shortness of breath, and hemoptysis in 44% of patients. Each individual dimension of the EQ-5D-5L was maintained/improved from baseline in the majority of patients (82%-91%), and $\geq$ 32% reported complete resolution at least once during treatment.

Conclusions: QoL was improved/maintained in patients with advanced SCC NSCLC treated with nab-P/C induction therapy. These results continue to support nab-P/C as a treatment option in patients with SCC NSCLC, as was initially demonstrated in a subset analysis of the phase III registration trial. NCT02027428.

Clinical trial identification: NCT02027428

Legal entity responsible for the study: Celgene Corporation

Funding: Celgene Corporation

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1367P Quality of life (QoL) in elderly NSCLC patients (pts) treated with nab-paclitaxel/carboplatin (nab-P/C) in the ABOUND.70+ trial

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Background: Treatment of elderly pts with advanced NSCLC remains challenging, and the impact of therapies on QoL can be an important factor in clinical decisions. nab-P/C demonstrated efficacy in a subset of pts $\geq$ 70 yrs with NSCLC in a phase 3 trial.

ABOUND.70+ was designed to determine whether a 1-wk break can further improve tolerability of nab-P/C in these patients. QoL outcomes are reported here.

Methods: Pts ≥ 70 yrs with locally advanced/metastatic NSCLC were randomized 1:1 to first-line nab-P 100 mg/m^2 on d 1, 8, and 15 + C AUC 6 on d 1 of a 21-day cycle (Arm A) or the same regimen with a 1-week break between cycles (Arm B). Primary endpoint: percentage of pts with grade ≥ 2 peripheral neuropathy or grade ≥ 3 myelosuppression. Key secondary endpoints: PFS, ORR, OS for which statistical analyses do not control for type I error (P values unadjusted). QoL (exploratory endpoint) was assessed using Lung Cancer Symptom Scale (LCSS) and EuroQoL-5 Dimensions-5 Levels (EQ-5D-5L) at d 1 of each cycle.

Results: At interim evaluation, primary endpoint was similar across arms, resulting in early closure of enrollment. In Arms A and B, 78% and 79% completed a baseline and ≥ 1 postbaseline QoL assessment. LCSS item of cough improved with each cycle; at the end of cycle 6, mean change from baseline in Arms A and B was 25.4 and 13.8 mm (visual analog scale). For cough, median time to deterioration (TTD) was 4.4 and 4.7 mos (P = 0.7003). For the composite LCSS pulmonary symptom items of cough, shortness of breath, and hemoptysis, the median TTD was 4.4 and 6.0 mos (P = 0.3347). Mean maximum improvement (at any point during treatment) in EQ-5D-5L visual analog scale was 10.1 and 12.8 points. Table lists key safety, efficacy and QoL data.

Table: 1367P

	Arm A n = 71	Arm B n = 72
Safety		
Primary endpoint, n (%)	52/68 (76)	54/70 (77)
P value	0.9258	
Grade ≥ 2 peripheral neuropathy	25/68 (37)	25/70 (36)
Grade ≥ 3 myelosuppression	48/68 (71)	45/70 (64)
Neutropenia	39/68 (57)	39/70 (56)
Anemia	14/68 (21)	17/70 (24)
Thrombocytopenia	17/68 (25)	12/70 (17)
Efficacy		
Confirmed ORR, %	24	40
P value	0.0376	
PFS, median, months	3.6	7.0
P value	0.0019	
HR (95% CI)	0.48 (0.30 - 0.76)	
OS, median, months	15.2	16.2
P value	0.1966	
HR (95% CI)	0.72 (0.44 - 1.19)	
QoL		
Mean maximum improvement from baseline, mm		
LCSS Total score	5.8	11.7
LCSS Pulmonary symptom	9.2	14.9

Conclusions: These results support nab-P/C as a treatment option in elderly pts with NSCLC. Safety (primary endpoint) and OS were similar across the two arms, while there was a signal of improvement in ORR, PFS, and QoL with a 1-wk break. NCT02151149.

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1368P Phase I/II trial of weekly nab-paclitaxel as 2nd or 3rd line treatment in NSCLC without driver mutations. (OLCSG1303)

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Background: Although nab-PTX plus carboplatin is one of the standard treatment for chemo-naive advanced non-small cell lung cancer (NSCLC), the efficacy, safety and optimal schedule of nab-PTX monotherapy as 2nd or 3rd line for NSCLC pts without any driver mutations remains unknown.

Methods: This was a single arm phase I/II study. Eligible pts are advanced NSCLC without EGFR mutation and ALK rearrangement that progressed after platinum-doublet chemotherapy. The pts were received 100 mg/m^2 of nab-PTX on day 1, 8, 15 and 22 (level 0) or on day 1, 8, and 15 (level -1) every 4-week in phase I. Dose limiting toxicities (DLT) were assessed and the recommended schedule was determined in the phase I. The primary endpoint was objective response rate (ORR), assuming that estimated ORR was 15% and threshold ORR was 5% with α error of 0.05 and β error of 0.2 in the phase II part. Total 55 pts were planned to be enrolled.

Results: The recommended schedule of nab-PTX was determined as the level -1, because the DLTs were found in 4 of 5 pts in level 0. Total 55 pts were enrolled in the phase II and the characteristics were as followings; median age, 66 years (range, 41–90 years), male/female = 40/15, PS 0/1/2 = 12/39/4, 2nd/3rd line = 34/21, adeno/squamous/large/others = 34/17/2/2. The median number of treatment cycles was three (range, 1–10). The ORR was 7.3% (95% [CI], 2.0 – 17.6%) (PR (n = 4), SD (n = 26), PD (n = 24), and NE (n = 1)). At the median follow-up time of 5.3 months (range, 1.9 – 26.0 months) for all pts, the median PFS was 3.4 months (95%[CI], 1.9 – 4.0 months). Treatment related grade 3 or 4 toxicities were neutropenia (36%), pulmonary infection (3.6%), and pneumonitis (5.4%). One patient (2%) was died due to treatment-related ARDS.

Conclusions: In phase I part, we confirmed that schedule level -1 was tolerable and the schedule had been recommended. In phase II part, this study failed to meet predefined primary endpoint although PFS was comparable and toxicity was acceptable for pts with advanced NSCLC without any driver mutations as 2nd or 3rd line treatment.

Clinical trial identification: UMIN000012404.

Legal entity responsible for the study: Okayama Lung Cancer Study Group

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1369P nab-paclitaxel/carboplatin (nab-P/C) induction therapy in squamous (SCC) non-small cell lung cancer (NSCLC): Interim safety results from ABOUND.sqm

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Background: The ABOUND.sqm trial is currently investigating treatment outcomes of 4 cycles of nab-P/C followed by nab-P maintenance therapy in patients (pts) with SCC NSCLC. Given that tolerability is an important consideration for treatment decisions, this analysis evaluated the safety of nab-P/C during induction.

Methods: Chemotherapy-naive pts with stage IIIB/IV SCC NSCLC received 4 cycles of induction therapy with nab-P 100 mg/m^2 d1, 8, and 15 + C area under the curve 6 d 1 (21-d cycles). Pts not progressing after induction received (2:1) maintenance nab-P 100 mg/m^2 d1 and 8 (21-d cycles) + best supportive care (BSC) or BSC alone until progression/unacceptable toxicity. The primary endpoint is progression-free survival (randomization to maintenance). Secondary endpoints include safety analyzed as treatment-emergent adverse events (TEAEs), overall survival, overall response rate, and disease control rate.

Results: A total of 334 pts were included in this analysis. Median age was 68 yrs; 90% were white, 68% male, and 68% had ECOG PS 1. During induction, 145/334 pts (43%) discontinued treatment. Of these, 51/145 (35%) discontinued due to progressive disease, 39/145 (27%) due to adverse events, 16/145 (11%) each due to death and pt withdrawal, 13/145 (9%) due to symptomatic deterioration, 9/145 (6%) due to other, and 1/145 (< 1%) due to protocol violation. The median percentage of per-protocol dose of *nab*-P was 74%; median *nab*-P dose intensity and cumulative dose were 74.08 mg/m^2/week and 900 mg/m^2, respectively. *nab*-P dose modifications included ≥ 1 reduction, missed dose, or dose delay in 55%, 60%, and 60% of pts, respectively. Grade ≥ 3 TEAEs were mainly hematologic and included neutropenia (148/334 [44%]), anemia (92/334 [28%]), and thrombocytopenia (48/334 [14%]). Grade ≥ 3 peripheral neuropathy was observed in 14/334 pts (4%).

Conclusions: This interim analysis demonstrates the safety and tolerability of nab-P/C induction therapy in pts with SCC histology. The findings are consistent with those reported in subset analysis of the phase III study and provide additional support for the use of this regimen in this pt population. NCT02027428.

Clinical trial identification: NCT02027428

Legal entity responsible for the study: Celgene Corporation

Funding: Celgene Corporation

Disclosure: C. Gridelli: Honoraria: Celgene. D. Morgensztern: Advisory role: Celgene; Speaker bureau: Boehringer. O. Juan: Advisory or Speaker role: Roche, Astra, MSD, Boehringer, BMS, Lilly, Pfizer, Pierre-Fabre. B. Levy: Honoraria: Eli Lilly, Genetech, Astra-Zeneca, Celgene; Consulting or Advisory Role: Eli Lilly, Genetech, Astra-Zeneca, Celgene; Speakers' Bureau: Eli Lilly, Genetech. A. Ardizzoni: Honoraria: Eli Lilly, BMS, MSD, Boehringer; Consulting Role: Eli Lilly, BMS, MSD, Boehringer. T. Berry: Employment and Stock Ownership: Celgene. T. Chen, N. Trunova: Employment and stock ownership: Celgene. All other authors have declared no conflicts of interest.

1370P Comparison of platinum agents cisplatin and carboplatin in routine treatment of advanced NSCLC: Results from prospective German TLK cohort study

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Background: Lung cancer is the leading cause of cancer-related mortality and the majority of patients (pts) are diagnosed with advanced or metastatic disease. Despite advances in targeted therapies for selected patient subgroups, the majority of pts (∼80%) are treated with platinum-based doublet chemotherapies (CT). The choice between the platinum agents cisplatin (CIS) or carboplatin (CAR) has been subject of a long debate. Here we present data on the treatment of advanced non-small cell lung cancer (aNSCLC) in routine practice. Such real-world data are of central importance to improve the standard of care.

Methods: 107 sites in Germany recruited 1,239 pts with aNSCLC at start of 1st-line therapy into the prospective clinical cohort study TLK (Tumour Registry Lung Cancer) between Feb 2010 and Dec 2013. Details on systemic treatment and outcome were collected until Jan 2016. A longitudinal health-related quality of life (HRQOL) analysis using the questionnaires EORTC QLQ-C30 and –LC13 was conducted every 2 months (mts) for a period of up to 10 months.

Results: 46% of the pts received CAR- and 35% CIS-based doublet CT in 1st-line treatment. Pts receiving CIS- were younger than pts receiving CAR-combinations (median age at start of treatment 62 vs. 69 years), more often had a good performance status (33% vs. 17% ECOG =0) and less comorbidities (34% vs. 56% Charlson Comorbidity Index ≥1). The main combination partner was pemetrexed for CIS (33%) and paclitaxel for CAR (24%). Median overall survival was 11.9 mts (95% CI 10.2-13.8) for CIS- and 12.2 mts (95% CI 10.0-13.3) for CAR-combinations. The median time to deterioration of the global health status was 6.8 mts for CIS- and 6.4 mts for CAR-combinations. Considerable deteriorations in the symptoms nausea, fatigue, dyspnoea and pain were reported after 4-6 mts, with no difference between CIS and CAR.

Conclusions: Numerous meta analyses have been dedicated to finding the optimal platinum agent for the 1st-line treatment of aNSCLC. With our data from the prospective, population-based cohort study TLK, we complement the results from clinical trials. We show that there is no considerable difference in outcome or HRQOL between CIS- and CAR-combinations in the treatment of aNSCLC.

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Legal entity responsible for the study: iOMEDICO AG

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1371P Diagnostic and therapeutic strategies for elderly patients with advanced non-small cell lung cancer (NSCLC): Results from an EORTC pan-European survey

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Background: The EORTC Lung Cancer Group (LCG) and the Elderly Task Force (ETF) developed a pan-european survey that aims to provide an overview of the management and treatment strategies for elderly patients (pts) diagnosed with advanced NSCLC, as well as to identify potential needs and scientific pending questions that could be addressed in new trials.

Methods: An electronic 13-topic survey explaining the study purpose was developed and sent to all EORTC LCG and ETF members. The 25-items included multiple-choice and open-ended questions requesting the following information on general demographics (6 items), pts population (3 items) and diagnostic, treatment preferences and outcomes (4 items). Elderly pts were defined as those older than 70 years.

Results: Sixty-two individual sites, from 19 countries, completed the online questionnaire. In 42 centers (67.7%) there is no dedicated team for the management and treatment of elderly pts; on the other hand, only in 2 centers (3.2%) pts with suspected NSCLC are not discussed by a multidisciplinary board. Notably, oncogeriatric assessment is routinely performed in 17 (27.4%) centers; G8, CGA or both scales are the preferred evaluation tools (35.3%, 23.6% and 11.8% respectively). In fit pts, the preferred first-line chemotherapy regimens are Carboplatin (CBDCA)-Pemetrexed (PEM) 19 (31.7%), CBDCA-Paclitaxel (PAC) 15 (24.2%), Cisplatin (CDDP)-PEM 14 (22.6%), CBDCA-Gemcitabine (GEM) 10 (16%), other 3 (4.8%). In the second line setting the preferred treatments are Nivolumab 30 (45.5%), PEM 11 (16.7%), Docetaxel 9 (13.6%), PAC 8 (12.1%), GEM 4 (6.1%), Erlotinib 4 (6.1%); while PEM 15 (24.2%), Nivolumab 13 (20.1%), PAC 9 (14.5%), Docetaxel 6 (9.7%), GEM 6 (9.7%), other 11 (17.7%) represent a second level option.

Conclusions: The survey provides an overview of the clinical practice in the management of elderly patients with advanced NSCLC, summarizing relevant and updated background for the possible development of future collaborative trials. In this survey, different treatment regimens are used by different centers, and geriatric assessment is used heterogeneously, reflecting the lack of a "standardized" approach and the need for further research in this area.

Legal entity responsible for the study: EORTC

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Disclosure: All authors have declared no conflicts of interest.

1372P Diversity of brain metastasis (BM) management in non-small cell lung cancer (NSCLC) in Europe (EU): Results of the Young Investigators European Organisation for Research and Treatment of Cancer Lung Cancer Group (YI EORTC LCG) survey

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Background: BM are frequent in NSCLC patients (pts) but management can vary.

Methods: An online survey containing questions on NSCLC BM screening and treatment (tx) was widely distributed between 16/02/17 and 16/04/17 to all EORTC LCG members, and through several EU societies involved in lung cancer tx.

Results: 478 physicians (phys) (radiation oncologist: 51.9%, pulmonologist: 27%, medical oncologist: 15.3%, others: 5.8%; 73.2% with >5 years experience in NSCLC) responded. Italy [17.8%], Netherlands [14.2%], UK [13.0%], and France [11.5%] contributed most. 84.9% screened neurologically asymptomatic pts for BM at diagnosis (49% used MRI). Phys screened stage III (66.9%) and IV (40.8%) most often. 35.4%

used a prognostic (p) classification to guide initial tx decisions. In 48.1% lowest p-score threshold to actively treat pts did not differ between driver mutation (MUT+) and non-driver (MUT-) pts. 38.1% used less WBRT in poor prognosis pts based on QUARTZ trial (NCT3826061) results. 88.9% had access to stereotactic radiosurgery (SRS). After single BM surgery, 50.8% systematically prescribe adjuvant SRS or WBRT, and 44.2% only in case of incomplete resection. Preferred tx in neurologically asymptomatic tx-naive pts diagnosed with >5 BM was systemic tx (78.4%). 46.9% stated that WBRT could increase systemic tx efficacy. 44.8/49.8% stated that all tyrosine kinase inhibitors (TKI) and immune checkpoint blockers (IO) were discontinued (timing varied) during SRS/WBRT, respectively. Drugs that were most often continued during SRS-WBRT were erlotinib (44.5-40.1%), gefitinib (38.0-34.0%), afatinib (29.9-25.1%), crizotinib (32.2-26.7%) and IO (PD-(L)-1: 28.4-22.8%), CTLA4: 10-9.8%), because of no perceived safety issues (44.6%) or risk of systemic flare (37.9%). MUT+ pts with > 3 BM were more likely to receive SRS than MUT-. 76% of phys preferred local tx & TKI continuation over a switch to next-line tx in pts with only intracranial progression.

Conclusions: BM management differs: screening is not uniform, p-classifications are not often used, and MUT+ NSCLC pts generally receive more aggressive local tx.

Legal entity responsible for the study: EORTC Lung Cancer Group

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Disclosure: All authors have declared no conflicts of interest.

1373P Clinical features of never smoker patients with lung squamous cell carcinoma: A retrospective multicenter study

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Background: Squamous cell carcinoma of the lung (LSCC) is the second most common histological subtype of non-small cell lung cancer (NSCLC) having smoking habit as the major risk factor. LSCC in non-smokers is an exceptional finding possibly related to professional exposure and subsequent carcinogenesis even though clinical and biological landscape is largely unexplored.

Methods: This is a retrospective multicenter study investigating clinical features of never-smoker LSCC patients (pts) referred to three Italian Centers between 2010 and 2016. Relapse (RFS) or progression free (PFS) and overall (OS) survival curves were calculated by Kaplan-Meier method. Cox regression proportional hazards model was used to estimate the impact of covariates on OS.

Results: Among 791 LSCC pts, 37(4,6%) occurred in never-smokers; our case series included 19 males and 18 females with a median age of 63 years. ECOG PS was 0-1 in 30(81%) pts. Median Charlson Comorbidity Index (CCI) was 6. Two (5%) pts referred second-hand smoking history and 13(35%) occupational exposure. Additional tumor history was reported by 15(41%) patients: head and neck (N=4), basocellular skin (N=5), breast (N=2), lung (N=2), prostate (N=1) cancer and leukemia (N=1). Molecular characterization was performed in 12(32%)pts: EGFR and KRAS mutations were found in 2 and 1 pts respectively. Median time from symptoms appearance and diagnosis was 7 weeks. Twelve (32%) pts showed a limited stage, while the other 25(68%) showed advanced/metastatic disease at the diagnosis. Nineteen (52%) pts received a first-line palliative chemotherapy (pct), mostly platinum-based doublets plus gemcitabine (N=11) or taxane (N=3), achieving a response rate and disease control rate of 37% and 58% respectively. Median RFS in resected patients (N=9) was 21 months. Median PFS and OS after first-line pct were 5 months and 8.5 months respectively. No covariate significantly impacted on OS.

Conclusions: Never-smoker LSCC pts represent a rare subgroup characterized by more females, younger age and a not negligible CCI and second-tumor history compared with the known features of smoker LSCC. Treatment outcome of advanced disease is still dismal as for most LSCC pts.

Legal entity responsible for the study: Istituto Oncologico Veneto IRCCS

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1374P Characteristics and prognostic impact of advanced non-small-cell lung cancer patients who were ineligible for clinical trials

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Background: The majority of non-small cell lung cancer (NSCLC) patients are ineligible for clinical trials. Nevertheless, very few studies report the profiles and treatment outcomes of such ineligible patients. Therefore, we investigated the characteristics, outcomes, and survival of advanced NSCLC patients who were ineligible for clinical trials.

Methods: We analyzed a retrospective cohort of 786 consecutive patients diagnosed with advanced NSCLC between January 2006 and December 2014. We reviewed the criteria in phase 3 clinical trials, and classified patients using the common first-line eligibility criteria for lung cancer.

Results: Of the 786 patients, 469 (60%) were ineligible for clinical trials. The main reasons for ineligibility were brain metastasis (41%), a poor performance status (PS) (25%), and respiratory disease (24%). In all patients, ineligibility was identified as an independent predictor of overall survival (OS) (adjusted hazard ratio [HR] 0.78, 95% confidence interval [CI], 0.65–0.93, P = 0.008), even in patients with a good PS who received chemotherapy (HR 0.80, 95% CI, 0.65–0.99, P = 0.037). In subgroup analyses of ineligible patients, the survival varied depending on the reasons for their ineligibility. In particular, prior cancer history was not associated with a poor outcome, though this was a common reason for ineligibility (14.5%).

Conclusions: Most patients were ineligible for clinical trials and had shorter survival. The survival of ineligible patients varied depending on the reasons for their ineligibility. We should consider these results when applying clinical trial outcomes to real-world patients. More studies for ineligible patients are needed to improve real-world treatment.

Legal entity responsible for the study: Daichi Fujimoto

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1375P Treatment paradigm shift in NSCLC: Patient data analysis from 2005 to 2016

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Background: In the last decade, chemotherapies were the SoC in advanced NSCLC treatment with limited benefit to long-term survival. Discovery of EGFR/ALK and PD1/PDL1 followed by of approval targeted therapies (TTs) and immunotherapies (IOs), respectively, marked two major treatments shifts. In addition, science advancement on drug resistance issued from TTs and new drug gable mutations continue to transform the treatment landscape and options for patients with advanced NSCLC.

Methods: This study used IMS Oncology Analyzer^{TM} a syndicated, retrospective, longitudinal cancer treatment database collecting anonymized patient-level oncology data in EU5, projected to national level. Data collected between 2005 and 2016 was used to identify changes in the treatment paradigm in advanced NSCLC. Three time period groups have been compared: period 1: from 2005 to 2008; period 2: from 2009 to 2014 and period 3: 2015 and 2016.

Results: Of the currently 1,602,026 (projected number) treated populations, there is an increase in protein kinase Inhibitors (TKIs) usage, mainly represented by anti EGFR and anti ALK, from 8% to 23% to 30% in period 1, 2 and period 3 respectively. Monoclonal antibodies (MAb) follows a similar trend increasing from 1% to 15% in the last years, respectively, while the platinum agents slightly decreases. IOs captures 52% in the last couple of years from the overall MAb group. Till recently, bevacizumab (BEVA) was leading this therapeutic class. Increased granularity in patient stratification, will allow identification of more spectacular treatment changes or identification of those who would have passed unnoticed. In 1L, mutant segment, paradigm switch occurred end 2008 when TKIs reached directly 84%. In 2L, IOs jump is much less noticeable, entering directly in the last analyzed period with 25% from MAb group. In WT segment, we can notice 2 switches: one in 1L, end 2014 when BEVA reached directly 13% and a second one in 2L, end 2016, when MAbs captured 28%, with IOs representing 90% from this therapeutic group.

Conclusions: Currently, the advent of IOs has completely overshadowed existing TTs. Emerging genetic markers (ROS-1, KRAS, RET), specific EGFR/ALK mutations due to resistance along with combinations of IOs and TTs will continue to add new treatment options.

Legal entity responsible for the study: QuintilesIMS

Funding: QuintilesIMS

Disclosure: All authors have declared no conflicts of interest.

1376TiP Phase III study of atezolizumab (atezo) vs chemotherapy (chemo) in patients (pts) with treatment-naive advanced, recurrent or metastatic NSCLC unsuitable for platinum (plat)-based chemo

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Background: Most pts with newly diagnosed NSCLC have locally advanced or metastatic disease, with 30%-40% having poor performance status (ECOG PS $\geq$ 2) due to

disease burden and comorbidities. These pts have poor prognosis vs pts with PS < 2 and higher toxicity with standard doublet chemo. Despite limited efficacy, single-agent chemo (vinorelbine [vin], gemcitabine [gem], docetaxel [doc]) is often used for pts who do not tolerate plat-based regimens, highlighting the need for new treatments. Atezo (anti–PD-L1) prevents PD-L1 from binding its receptors PD-1 and B7.1, restoring cancer-specific T-cell immunity. In OAK, a Phase III 2L+ NSCLC study, atezo monotherapy was well tolerated and showed significant OS improvement vs doc regardless of PD-L1 status. Thus, atezo could provide superior clinical benefit vs single-agent chemo and demonstrate a more favorable safety profile in these pts. The open-label, randomized, multicenter Phase III PS2 study will evaluate the efficacy and safety of atezo vs single-agent chemo (vin, gem) in pts with untreated advanced, recurrent or metastatic NSCLC unsuitable for plat-based chemo.

Trial design: Eligible pts have Stage IIIB/IV NSCLC; are considered unsuitable for plat-based chemo due to poor PS (ECOG PS 2-3); have substantial comorbidities or contraindications for plat-based doublet chemo; have measurable disease; have no *EGFR*/*ALK* mutations and have received no prior systemic therapy. Pts will be randomized 2:1 to receive atezo 1200 mg IV q3w or single-agent chemo (vin [PO/IV], gem [IV]) per local practice until PD. Pts on atezo may continue therapy until loss of clinical benefit. Stratification factors include histology subtype (squamous vs nonsquamous), PD-L1 status (by VENTANA SP142 IHC assay) and presence of brain metastases. Primary endpoint is OS. Secondary endpoints include OS at 6, 12, 18 and 24 mo; ORR; PFS; DOR and safety. Tumor biopsies and blood samples (pre-treatment all mandatory; at PD only blood mandatory) will be assessed for biomarkers associated with atezo responses and immune escape. Planned enrollment is ≈ 441 pts.

Clinical trial identification: NCT pending (available on poster)

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

Funding: F. Hoffmann-La Roche Ltd.

Disclosure: S.M. Lee: Advisory Board for Roche, Merck, Bristol-Myers, Astra Zeneca. C. Schulz: Scientific Advisor or Membership: AstraZeneca, BMS, Boehringer, Lilly, Novartis, Roche Honoraria: AstraZeneca, Celgene, BMS, Boehringer, Lilly, Novartis, Roche. A. Cardona: Roche employee. P. Bartakova: F. Hoffmann-La Roche employee and company stock ownership. S. Peters: Edu grants, consultation, AB, lectures: Amgen, AZ, BI, BMS, Clovis, Eli Lilly, F. Hoffmann-La Roche, Guardant health, Janssen, Merck Sharp and Dohme, and Merck Serono, Merrimack, Morphotek, Pfizer, Regeneron, Takeda.

1377TiP JAVELIN Lung 100: updated design of a phase 3 trial of avelumab vs platinum doublet chemotherapy as first-line (1L) treatment for metastatic or recurrent PD-L1+ non-small-cell lung cancer (NSCLC)

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Background: Avelumab is a human anti–PD-L1 IgG1 antibody that has shown promising antitumor activity and manageable safety in several tumor types, including NSCLC, and is approved in the US for the treatment of metastatic Merkel cell carcinoma. Reports with anti–PD-(L)1 therapies suggest a role in 1L treatment of NSCLC using tumor PD-L1 expression selection criteria; however, optimal treatment for patients (pts) with different PD-L1 expression status is currently undefined. Preliminary exposure-response analysis from pts with NSCLC treated with avelumab 10 mg/kg Q2W in the JAVELIN Solid Tumor trial (NCT01772004) suggest enhanced antitumor activity with higher avelumab exposure. This phase 3 trial (NCT02576574) compares avelumab vs platinum doublet chemotherapy as 1L treatment for PD-L1+ NSCLC. Here, we describe the updated design, including an additional treatment arm to investigate the role of higher avelumab exposure in this setting.

Trial design: JAVELIN Lung 100 is an ongoing global, multicenter, randomized, open-label trial. The study protocol has been amended to demonstrate superiority of avelumab in prolonging PFS or OS as co-primary endpoints vs platinum doublet therapy, per RECIST v1.1 by blinded independent review. A hierarchical testing strategy will be applied to compare avelumab arms vs chemotherapy in terms of PFS and OS by PD-L1+ enriched populations (expression cutoff levels: high, moderate, and any, determined by the Dako 73-10 assay) at an overall significance level of 2.5% (one-sided). Eligibility criteria include: stage IV NSCLC, ECOG PS ≤ 1, no prior systemic treatment for advanced disease, and no EGFR mutation/ALK translocation. Approximately 1,095 pts will be randomized to 1 of 3 arms: arm A (avelumab 10 mg/kg 1-hour IV Q2W), arm B (investigator's choice of specified platinum-based chemotherapy), or arm C (avelumab 10 mg/kg every week for 12 weeks, then 10 mg/kg Q2W), stratified by NSCLC histology and baseline tumor PD-L1 expression level. Secondary endpoints include objective response, duration of response, safety, pt-reported outcomes, PK, and biomarker assessments.

Clinical trial identification: NCT02576574 Protocol number: EMR 100070-005

Legal entity responsible for the study: Pfizer Inc., New York, NY, USA and Merck KGaA, Darmstadt, Germany.

Funding: Pfizer Inc., New York, NY, USA and Merck KGaA, Darmstadt, Germany.

Disclosure: M. Reck: Advisory Role: Roche, Lilly, BMS, MSD, Merck, AstraZeneca, Boehringer Ingelheim, Pfizer, Novartis, Celgene. Speaker's Bureau: Roche, Lilly, BMS, MSD, Merck, AstraZeneca, Boehringer Ingelheim, Pfizer, Novartis, Celgene. C-H. Yang: Advisory Role: BI, Eli Lilly, Bayer, Roche/Genentech/Chugai, Astellas, MSD, Merck Serono, Pfizer, Novartis, Clovis Oncology, Celgene, Merrimack, Yuhan Pharmaceuticals, BMS, Ono pharmaceutical Daiichi Sankyo and Astrazeneca, Hansoh Pharmaceuticals. P.E. Postmus: Consulting: Celgene, BMS, Roche, Boehringer Ingelheim. Travel, Accomodations, expenses: Boehringer Ingelheim. Speaker's Bureau: Eli Lilly. F. Barlesi: Honoraria: Astra-Zeneca, Bristol-Myers Squibb, Boehringer–Ingelheim, Clovis Oncology, Eli Lilly Oncology, F. Hoffmann–La Roche Ltd, Novartis, Merck, MSD, Pierre Fabre and Pfizer. E.F. Font: Advisory Role: Eli Lilly, Pfizer, Roche, Boehringer Ingelheim, MSD. Speaker's Bureau: AstraZeneca, BMS, Novartis. M. Thomas: Grants/Research Support Recipient: Lilly, Pierre Fabre, BMS, AstraZeneca. Advisory Role: Lilly, Pierre Fabre, BMS, AstraZeneca, MSD, Novartis, Celgene, Roche, Pfizer. Honoraria: Lilly, MSD, Celgene, Roche. R. Sullivan: Travel, accommodations, expenses: BMS and Roche. N. Pavlakis: Grants/Research Support: Bayer. Advisory Role: Bayer, BI, AZ, MSD, BMS, Roche, Pfizer, Amgen, Merck Serono. L.M. Dreosti: Grants/Research Support: Novartis. Advisory Role: Novartis, Roche. Honoraria: MSD, Novartis, Janssens. Congress sponsorship: Roche, Merck, Janssens M. Özgüroğlu: Advisory Role: Sanofi. M. Schlichting: M.S. is an employee of Merck KGaA, Darmstadt, Germany. F. Teofilovici: F.T. is an employee of EMD Serono Inc. V. Chand: V.C. is an employee of EMD Serono Inc. V.C holds Bristol Myers Squibb stock. V. Westeel: Research funding: Roche, Genentech, BI, Merck Serono. Expert Testimony: Teva. Consulting: Pierre-Fabre Onc, MSD, Eli Lilly, AZ, BI, Novartis. Travel: Pierre-Fabre Onc, Roche, BMS, Eli Lilly, Merck Serono, Pfizer, BI. Speaker's Bureau: AZ, MSD, BMS, BI. All other authors have declared no conflicts of interest.

1378TiP A phase 3 study of first-line durvalumab vs platinum-based chemotherapy in patients with advanced NSCLC and high PD-L1 expression: PEARL

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Background: NSCLC is highly prevalent in Asia. Differences in outcomes to therapy, including longer survival and higher response rates, have been noted in Asian vs Caucasian NSCLC patients due to the higher prevalence of targetable oncogenes (i.e. *EGFR* sensitizing mutation or *ALK* translocation) in the Asian population. Until recently, standard of care (SoC) first-line treatment of *EGFR*/*ALK* wild-type advanced NSCLC comprised systemic platinum-based doublets. However, over recent years, immune checkpoint blockade has also become an important option, including in the first-line setting where pembrolizumab is approved in the US, EU and Japan in patients whose tumours express high levels of PD-L1. Durvalumab is a selective, high-affinity, anti-PD-L1 antibody that has shown antitumour activity and manageable tolerability across multiple tumour types, including NSCLC. The PEARL study aims to assess first-line durvalumab vs SoC in predominantly Asian populations with *EGFR*/*ALK* wild-type advanced NSCLC and high tumour PD-L1 expression.

Trial design: PEARL (NCT03003962) is a randomised, open-label, multicentre Phase 3 study. Eligible patients are immunotherapy- and chemotherapy-naïve with Stage IV, *EGFR*/*ALK* wild-type NSCLC, high PD-L1 expression (≥25% tumour cells with membrane staining using the Ventana PD-L1 [SP263] Assay) and ECOG performance status of 0 or 1. ~440 patients will be stratified by level of PD-L1 expression, histology and smoking status, and randomised 1:1 to receive either durvalumab (20 mg/kg i.v. every 4 weeks [q4w]) or SoC platinum-based chemotherapy until disease progression. The co-primary endpoints are PFS using blinded independent central review assessments according to RECIST v1.1 and OS. Secondary endpoints include ORR; duration of response; proportion of patients alive and progression free at 12 months; PFS after subsequent anticancer therapy; disease-related symptoms and HRQoL; immunogenicity; safety (CTCAE v4.03) and tolerability. Tumour assessments will be performed q6w for the first 48 weeks and then q8w as defined by RECIST v1.1 until confirmed

disease progression. Recruitment is ongoing in Australia, China, Republic of Korea, Russia, Thailand and Vietnam.

Clinical trial identification: NCT03003962 (release date: December 15, 2016)

Legal entity responsible for the study: AstraZeneca PLC

Funding: AstraZeneca

Disclosure: Y-L. Wu: Speaker fees: Roche, AstraZeneca, Eli Lilly, Sanofi, Pfizer. S. Lu: Speakers' Bureau: AstraZeneca, Eli Lilly, Roche, Sanofi Corporate sponsored research: AstraZeneca, Boehringer-Ingelheim, Hutchison, Roche Consultant: AstraZeneca, Boehringer-Ingelheim, Hutchison, MediPharma, Roche. S. Clarke: Corporate sponsored research: Ipsen, Merck Honoraria: AstraZeneca, Ipsen, Merck. K. Lactionov: Consultant BMS, AstraZeneca, MSD, Pfizer and travel grants BMS, AstraZeneca, MSD, Pfizer P. Li, M. Kirkby, P. Stockman: AstraZeneca: full-time employment and stock ownership. Y. Xie: AstraZeneca: full-time employment.

1379TiP Phase I/II study of S 49076, a MET/AXL/FGFR inhibitor, in combination with gefitinib in EGFR-mutated NSCLC patients who progress on EGFR tyrosine kinase inhibitor

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Background: EGFR-mutated NSCLC patients treated with EGFR TKI ultimately develop resistance to therapy. Mechanisms of resistance include aberrant signalling of MET, AXL and FGFR. Inhibition of these receptors should thus abrogate their downstream signalling and restore sensitivity to EGFR TKI. S 49076 is a potent ATP-competitive TKI, which targets MET, AXL and FGFR1/2/3 at clinically relevant doses. It showed strong activity in preclinical assays against EGFR mutated MET amplified cell lines to overcome the resistance to EGFR TKI. This study evaluates the relevance of targeting MET and/or AXL dysregulation to overcome acquired non EGFR-T790M-mediated resistance to EGFR-TKI.

Trial design: The phase I/II is an international, open-label study to evaluate the safety and activity of S 49076 in combination with gefitinib in stage IIIb-IV NSCLC patients who progress on EGFR TKI (1st and 2nd generation), harbouring MET and/or AXL dysregulation without EGFR-T790M mutation. The phase I is a single arm dose-finding part of S 49076 in combination with standard dose of gefitinib. The primary objective is to determine the recommended phase 2 dose (RP2D) based on the dose-limiting toxicities and safety assessments. The secondary objectives are to evaluate the pharmacokinetic profile of both drugs and the anti-tumour activity of the combination. S 49076 and gefitinib are administered orally once daily over a continuous 28-day cycle with doses ranging from 500mg to 600mg. Dose levels are allocated using a modified Bayesian Continual Reassessment Method. This study part is active and recruiting over 5 countries across Asia and Europe. The end of phase I is expected in Q3 2017. A non-randomised and non-comparative phase II part will then evaluate the anti-tumour activity of S 49076 at the RP2D in combination with gefitinib in cohorts of patients with MET and/or AXL dysregulation. The primary objective will be to determine the objective response rate according to RECIST and the secondary objectives will be to evaluate survival rate, progression free survival, clinical benefit rate and response duration as well as safety. An interim analysis will be performed in each cohort for futility.

Clinical trial identification: EudraCT 2015-002646-31

Legal entity responsible for the study: Institut de Recheches Internationales Servier

Funding: Institut de Recherches Internationales Servier

Disclosure: K. Park: Servier study international coordinator and investigator. F. Ciardiello, W. Lim, C-C. Lin: Servier study national coordinator and investigator. T. Hida, H. Murakami, M. Nishio: Servier study investigator. F. Cantero, V. Cattan, C. Gabarroca, E. Gandossi: Servier employee. L. Paz-Ares: Study Servier national coordinator and investigator.

1380TiP A randomized, open-label comparison of lorlatinib versus crizotinib as first-line treatment for advanced anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer

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Background: Lorlatinib and crizotinib are oral tyrosine kinase inhibitors with activity against ALK and ROS1 fusion proteins. Crizotinib is well tolerated and has superior efficacy compared to chemotherapy for treatment of patients (pts) with advanced ALK^+ NSCLC. However, resistance to crizotinib can develop, and the central nervous system (CNS) is often a site of disease relapse. Lorlatinib is a CNS penetrant and has potent activity against de novo fusions and kinase domain resistance mutations. Lorlatinib has shown clinical activity in pts previously treated with crizotinib and other ALK inhibitors, including pts with progressive CNS metastases. This study aimed to determine if lorlatinib is superior to crizotinib in prolonging progression-free survival (PFS) in treatment-naïve pts with advanced ALK^+ NSCLC and to identify candidate biomarkers predictive of clinical efficacy or treatment resistance.

Trial design: This global, multicenter, open-label phase 3 study will enroll ~280 treatment-naïve pts. Eligible pts must be aged ≥18 years, have Eastern Cooperative Oncology Group performance status of 0–2 and ≥1 measurable extracranial target lesion not previously treated with radiotherapy. Pts with asymptomatic brain metastases are eligible. Pts will be randomized (1:1) to lorlatinib 100 mg once daily or crizotinib 250 mg twice daily and stratified by presence of brain metastases (yes/no) and ethnicity (Asian/non-Asian). Treatment will continue until disease progression, pt refusal, or unacceptable toxicity. Crossover between treatment arms will not be permitted. The primary endpoint is PFS based on blinded independent central review (BICR) using RECIST v1.1. Secondary endpoints include PFS based on investigator assessment (IA), overall survival, objective response (OR) by BICR and IA, intracranial (IC) OR, IC time to progression, duration of response, time to response by BICR, tumor tissue and peripheral blood circulating free DNA biomarker assessment, safety, and pt-reported health-related outcomes. The first pt was screened on April 14, 2017. This study is registered with ClinicalTrials.gov as NCT03052608.

Clinical trial identification: NCT03052608

Legal entity responsible for the study: Pfizer

Funding: Pfizer

Disclosure: A.T. Shaw: Membership of an advisory board or board of directors - Blueprint medicines, KSQ therapeutics. Honoraria or Consulting - Pfizer, Novartis, Ariad, Genentech/Roche, Ignyta, Daiichi-sankyo, Taiho, LOXO, Blueprint medicines, EMD Serono, Foundation Medicine. T. Takahashi: Corporate sponsored research - AstraZeneca, Pfizer, Eli Lilly, Chugai Pharmaceutical Co, Ono Pharmaceutical Other, please specify; Honoraria - AstraZeneca, Pfizer, Eli Lilly, Chugai Pharmaceutical, Ono Pharmaceutical. C.S. Baik: University of Washington: Pfizer; Novartis, Loxo Oncology, Genentech, MedImmune, Mirati Therapeutics, Clovis Oncology, GlaxoSmithKline, Eisai, Celgene, Bristol-Myers Squibb, Merck Sharp & Dohme Corp. Clovis Oncology and Novartis. A. Polli: Stock ownership - Pfizer. M. Carpentieri: Stock ownership - Pfizer Other relationships (such as employment) with a pharmaceutical company - Pfizer. J-F. Martini: Stock ownership - Pfizer Other relationships (such as employment) with a pharmaceutical company - Employee (Pfizer). B.J. Solomon: Membership of an advisory board or board of directors - Advisory Boards: Pfizer, Novartis, Roche-Genentech, AstraZeneca, Merck, Bristol Myers Squibb. All other authors have declared no conflicts of interest.

1381TiP A randomized double-blind phase II trial evaluating maintenance PARP inhibitor Olaparib versus placebo in patients with platinum-sensitive advanced non-small cell lung cancer: PIPSeN trial

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Background: Poly (ADP-ribose) polymerase inhibitors (PARPi) have demonstrated impressive efficacy in BRCA-mutated gynaecological malignancies. Several lines of evidence now support that the DNA repair (DDR)-deficient populations that benefit from PARPi go far beyond BRCA-deficiency. Non-small cell lung cancer (NSCLC), the first cause of cancer death worldwide, displays frequent DDR defects, the most frequent being ERCC1. This defect leads to platinum and PARPi sensitivity. Beyond ERCC1, DDR defects leading to platinum sensitivity widely overlap with those underlying PARPi sensitivity. Maintenance PARPi could therefore benefit to patients (pts) with platinum-sensitive NSCLC. Olaparib (Lynparza®, Astra Zeneca), a potent and selective PARPi, was the first-in-class approved PARPi in BRCA-mutated ovarian cancer.

Trial design: PIPSeN is a randomized double-blind phase II investigator-initiated study evaluating maintenance Olaparib versus placebo in pts with platinum-sensitive advanced NSCLC. Chemonaïve ECOG PS 0-1 pts with stage III-IV NSCLC with no *EGFR* mutation or *ALK* translocation are eligible. Treatment consists of an "induction phase" of 4-6 cycles platinum-based therapy (any doublet), followed by a "randomized phase" where pts presenting with partial or complete response are randomized between Olaparib maintenance (tablets; 300mg bd) and placebo until progression or unacceptable toxicity. Primary objective is to assess the efficacy of maintenance Olaparib as measured by Progression-Free Survival from randomisation (RECIST v1.1). Secondary objectives include comparison of overall survival, disease control rate and safety. Randomization is stratified according to age, histology and country. With an anticipated HR = 0.65 (bilateral $\alpha = 0.2$; $\beta = 0.2$), approximately 500 enrolled pts will be required to randomize 144 pts and observe 97 events. Recruitment is ongoing since the 5th of Feb. 2016 across 21 centres in France and Spain; 95 (19) pts have been enrolled (randomised) to date. Translational studies looking notably for biomarkers of platinum and PARPi sensitivity (using WES, RNAseq, proteomics and ctDNA) are associated.

Clinical trial identification: EudraCT: 2014-005586-75 NCT02679963

Legal entity responsible for the study: Gustave Roussy Cancer Campus (sponsor), in collaboration with the Spanish Lung Cancer Group

Funding: Astra Zeneca

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1382TiP Investigation of biomarkers in patients with adenocarcinoma of the lung receiving nintedanib according to approved label: Non-interventional LUME-BioNIS study

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Background: In the Phase 3 LUME-Lung 1 trial, the addition of nintedanib to docetaxel significantly improved overall survival (OS) vs docetaxel alone in patients with adenocarcinoma non-small cell lung cancer (NSCLC) treated with one prior line of chemotherapy. No tumour or serum biomarkers are validated to predict nintedanib efficacy in this setting.

Trial design: LUME-BioNIS (NCT02671422) is an ongoing, prospective, European, multicentre, non-interventional study (N≈300) investigating whether tumour-based genomic or proteomic alterations (± clinical covariates) can predict OS in adults with advanced adenocarcinoma NSCLC initiating nintedanib + docetaxel according to the nintedanib label. Tumour tissue obtained before first-line therapy will be used for biomarker analyses. To ensure sample quality and tumour content across all slides, the first, middle and last slides will be haematoxylin/eosin-stained and assessed by a certified pathologist for tumour content, extent of necrosis and immune cell infiltration. Tumour DNA and RNA will be co-isolated from unstained slides (AllPrep® DNA/RNA FFPE Kit) and quantitated with PicoGreen® and RiboGreen® reagents, respectively. Tumour DNA sequencing libraries will be prepared using a capture-based targeted gene panel covering whole exons of NSCLC-related genes (e.g. EGFR, KRAS, ALK, BRAF, PIK3CA, TP53) and nintedanib target genes (VEGFR1–3, FGFR1–3, PDFGR α/β) and analysed by Illumina® next-generation sequencing (NGS). Transcriptomics analyses will be conducted to: (1) complement DNA analyses by providing further information on gene fusions; and (2) enable tumour classification into transcriptional subtypes. Tumour RNA libraries will be prepared and analysed by NGS or, if RNA quantity/quality is insufficient for sequencing, digital gene expression analysis (nCounter® Gene Expression Panels) will be performed. Unstained slides will also be analysed by immunohistochemistry for immune- and proliferation-related protein expression (PD-L1, Ki-67). The primary endpoint is OS, which will be analysed according to biomarker status.

Clinical trial identification: NCT02671422

Legal entity responsible for the study: Boehringer Ingelheim Pharma GmbH & Co. KG

Funding: Boehringer Ingelheim Pharma GmbH & Co. KG

Disclosure: M. Reck: Author reports personal fees from Boehringer-Ingelheim, Hoffmann-La Roche, Lilly, MSD, BMS, AstraZeneca, Celgene, Merck and Pfizer. N. Morsli, K. Pietzko, T. Kitzing, J. Braunger: Author is an employee of Boehringer-Ingelheim. K.M. Kerr: Personal fees from Boehringer Ingelheim, during the conduct of the study. All other authors have declared no conflicts of interest.

1383TiP Blood first line ready screening trial (B-F1RST) and blood first assay screening trial (BFAST) enable clinical development of novel blood-based biomarker assays for tumor mutational burden (TMB) and somatic mutations in 1L advanced or metastatic NSCLC

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Background: Several clinical trials have confirmed the safety and efficacy of atezolizumab (atezo; anti–PD-L1) monotherapy in advanced NSCLC, including in PD-L1–selected 1L patients (pts). Independent of PD-L1 status, high TMB is associated with atezo efficacy. Alectinib is a potent, selective ALK/RET kinase inhibitor currently approved for NSCLC pts previously treated with crizotinib and is expected to have activity in 1L NSCLC pts with *ALK* or *RET* alterations. Currently, molecular diagnostics require tumor biopsies which can be difficult to obtain. Here we present trials in progress that aim to clinically evaluate and prospectively validate novel blood-based diagnostic assays that measure TMB in the blood (bTMB) and somatic mutations (e.g., *ALK*/*RET*), and to determine the efficacy and safety of 1L atezo or alectinib in NSCLC pts.

Trial design: B-F1RST (NCT02848651) is a single-arm study to evaluate the efficacy and safety of atezo and the association between bTMB and efficacy in biomarker-unselected pts. BFAST is a screening and interventional umbrella trial for pts selected based on bTMB or somatic mutations. Eligible pts must have previously untreated, stage IIIB-IVB NSCLC of any histology and measurable disease per RECIST v1.1. Pts will continue treatment until disease progression (all arms) or loss of clinical benefit (atezo only). In B-F1RST, mandatory blood samples will be prospectively collected and retrospectively tested for bTMB. In BFAST, pre-enrollment screening will identify pts who harbor oncogenic somatic mutations (*ALK*/*RET*) or are bTMB + (above a prespecified cutoff); pts will be assigned to the appropriate cohort based on screening results. Study treatments and key endpoints are shown in the table. Additional BFAST cohorts may be added in the future to address other somatic mutations.

Table: 1383TiP B-F1RST and BFAST Study Details

Study	Treatment	Planned Enrollment, n	Primary Endpoints	Key Secondary Endpoints
B-F1RST Phase II	Atezo 1200 mg IV q3w	150	ORR per RECIST v1.1 (INV-assessed) for the efficacy objective Relationship between PFS per RECIST v1.1 and various bTMB quantiles for the biomarker objective	PFS and DOR per RECIST v1.1 (INV-assessed) OS
BFAST Phase II/III				
Cohort A *ALK*+	Alectinib 600 mg PO bid	78	ORR per RECIST v1.1 (INV-assessed)	DOR, CBR and PFS per RECIST v1.1 (INV-assessed) ORR, DOR, CBR and PFS per RECIST v1.1 (IRF-assessed) OS
Cohort B *RET*+	Alectinib 900 mg & 1200 mg dose escalation	52-62	ORR per RECIST v1.1 (INV-assessed)	DOR, CBR and PFS per RECIST v1.1 (INV-assessed) ORR, DOR, CBR and PFS per RECIST v1.1 (IRF-assessed) OS
Cohort C bTMB+	Atezo 1200 mg IV q3w or platinum-based chemotherapy[a]	440 (R, 1:1)	PFS per RECIST v1.1 (INV-assessed)	OS PFS, ORR and DOR per RECIST v1.1 (IRF-assessed) ORR and DOR per RECIST v1.1 (INV-assessed) 6- and 12-month PFS rates

[a]Cisplatin or carboplatin + pemetrexed for non-squamous histology, and cisplatin or carboplatin + gemcitabine for squamous histology. Administered per standard of care. INV, investigator; IRF, independent review facility; R, randomized;
[b]TMB, blood Tumor Mutational Burden.

Clinical trial identification: NCT02848651, B-FAST NCT number available on poster

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

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Disclosure: T.S.K. Mok: Spt: AZ, BI, PFE, NV, SFJ, ROG, MSD, CLVS, BMS, Eisai, Taiho ROG/GNE, LLY, NV; Stock Sanomics AB: AZ, ROG/GNE, PFE, LLY, BI, CLVS, MSD, NV, SFJ, ACEA Bio, VRTX, BMS, GeneDecode, OGX, CELG, RXDX Bod: IASLC, CLCRF, CSCO, HKCTS. S. Gadgeel: Speaker's bureau- Astra-Zeneca, Genentech/Roche Advisory Boards- Astra-Zeneca, Ariad, Pfizer, Bristol Myers- Squibb and Genentech/Roche. E.S. Kim: Consulting or advisory role: AstraZeneca, Celgene, BI, Eli Lily. V. Velcheti: Consulting/advisory role: Genentech, BMS, Merck, AstraZeneca, Foundation Medicine, Genoptix, Amgen. S. Hu, D.S. Shames: Genentech employee and Roche stock. T. Riehl, E. Schleifman, S. Mocci, S. Phan, M. Mathisen: Genentech employee. S.M. Paul: Genentech employee, Roche Stock, Travel, Accommodations, Expenses from Genentech. C. Yun: Employee of Genentech, Roche stock, Research funding from Genentech. M. Kowanetz: Genentech employee & Roche stock. U. Sweere: Roche employee. M.A. Socinski: Honoraria: Genentech Speakers Bureau: Genentech Research Funding: Genentech.

1384TiP Prospective comparison of liquid biopsy to standard of care tissue testing in metastatic, non-squamous, non-small cell lung cancer (NSCLC) patients (pts)

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Background: Targeted therapy improves clinical outcomes in pts with advanced NSCLC harboring specific genetic alterations. Guidelines recommend tissue-based assessment of markers, but this approach may be limited by access to sufficient tissue and tumor heterogeneity, making it difficult to identify all pts who may benefit from these treatments. An alternative approach is to assess somatic mutations in circulating cell-free tumor DNA (cfDNA). The aim of this study is to demonstrate that cfDNA is non-inferior to tissue-based genotyping in detecting clinically actionable tumor biomarkers in pts with newly diagnosed metastatic non-squamous NSCLC.

Trial design: This is a multi-center, prospective, single-cohort study. Major inclusion criteria are: (1) metastatic, biopsy proven, non-squamous NSCLC, (2) candidate for first line systematic therapy, (3) no prior targeted therapy. Peripheral blood (20 mL) is collected for cfDNA sequencing prior to and 2 weeks after treatment initiation and at the time of disease progression (maximum 12 months follow-up). cfDNA sequencing is performed using Guardant360, a comprehensive next-generation assay (Guardant Health, Inc., Redwood City, CA USA). Pre-treatment tissue samples archived at local sites are centrally analyzed. Pts are treated according to investigator standard of care criteria. Tumor response is assessed centrally per RECIST v1.1 on pts who received targeted therapy. Primary endpoint is the detection rate, in either blood or tissue, of a clinically actionable somatic biomarker, defined as mutations in EGFR, BRAF, MET and ERBB2, copy number of MET and rearrangement of the ROS1, RET and ALK genes. A total of 182 pts are needed to test a 10% non-inferiority margin. We assumed a 20% detection rate, with a 19% discordant pairs and 10% dropout rate. The one-sided asymptotic test has 90% power, at a nominal significance level of 5%. Secondary objectives are to compare turn-around time, time to treatment initiation, rates of insufficient tissue for testing or tumor not detected in cfDNA, and tumor response to targeted therapies. Genomically acquired resistance to targeted therapies is also investigated.

Clinical trial identification: MedOPP125 (NCT number in progress)

Legal entity responsible for the study: Medica Scientia Innovation Research-MEDSIR

Funding: Guardant Health Inc.

Disclosure: S. Viteri: Research: AbbVie, ARIAD, Astex, AZ/MedImmune, Boehringer, Clovis, CytRx, Daiichi Sankyo, GSK, Hanmi, Incyte, Merck, Novartis, Pfizer, Puma, Roche, Servier, Vaxon. Advisor: Boehringer, Clovis, Idea Pharma, Novartis, Promega Biotech, Roche, Targovax. E. Felip Font: Personal fees (Consulting fees) from: Boehringer Ingelheim, Eli Lilly, Pfizer, Roche and MSD, Astra Zeneca and Bristol Myers Squibb. All other authors have declared no conflicts of interest.

1385TiP Clinical Research platform Into molecular testing, treatment and outcome of non-Small cell lung carcinoma Patients (CRISP): a prospective German Registry in stage IV NSCLC AIO-TRK-0315)

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Background: Treatment in NSCLC is quickly evolving and new agents make it to the routine practice at a rapid pace. Whether outcome and PRO data generated from clinical trials with often narrow inclusion and exclusion criteria will hold up in the routine practice is of high interest, especially due to the increasing costs of new drugs. Therefore registry data are of ever increasing importance to patients, physicians and reimbursement institutions.

Trial design: We have started a prospective, clinical registry to document representative data on molecular testing, sequences of systemic therapies and other treatment modalities, and course of disease in patients with metastatic NSCLC in Germany (CRISP, NCT02622581). A particular focus is on molecular biomarker testing of patients before the start of first-line treatment. The data shall be used to assess the current state of care and to develop recommendations concerning topics that could be improved. PRO assessment will provide large-scale data on quality of life and anxiety/depression for real-life patients in routine practice. In addition, two questionnaires (concerning individual quality of life and patient-caregiver communication) will be validated in German patients with metastatic NSCLC. Furthermore CRISP will set up a decentral tissue annotation for future collaborative, investigational scientific biomarker testing. CRISP will be carried out in up to 150 representative cancer centers in all therapeutic sectors in Germany. More than 5000 patients will be recruited and followed up until death or for a maximum of 3 years. The first patient has been included in December 2015. Currently, 104 centers have been initiated, and 765 patients have been recruited. Preliminary data will be presented at the meeting in terms of molecular test rates, demographic data as well as treatment stratification in the 1st line setting. In conclusion: The registry CRISP will be the first to present representative real life data, covering all treatment settings of patients with NSCLC in Germany. CRISP is supported by AstraZeneca, Boehringer Ingelheim, BMS, Celgene, Lilly, MSD, Novartis, and Pfizer.

Clinical trial identification: NCT02622581

Legal entity responsible for the study: AIO-Studien-gGmbH, Berlin

Funding: AstraZeneca GmbH, Boehringer Ingelheim Pharma GmbH & Co. KG, Bristol-Myers Squibb GmbH & Co. KGaA, Celgene GmbH, MSD Sharp & Dohme GmbH, Lilly Deutschland GmbH, Novartis Pharma GmbH, and Pfizer Pharma GmbH.

Disclosure: F. Griesinger: Advisory Board/Honoraria: Ariad, Astra-Zeneca, Boehringer-Ingelheim, Bristol-Myer-Squibb, Celgene, Clovis, Lilly, Merck-Sharp-Dome, Novartis, Pfizer, Roche N. Marschner: ADB: Amgen, Roche Honoraria: Amgen, Celgene, Roche research grants: Amgen, Celgene, stock ownweship/leadership position: iOMEDICO AG. M. Sebastian: Advisory boards: BMS, MSD, Roche, Novartis, AstraZeneca, Boehringer, Celgene, Lilly, Pfizer. M. Thomas: Honoraria/AD Boards: MSB, BMS, Lilly, Astrazeneca, Roche, Pfizer, Celgene, Novartis. All other authors have declared no conflicts of interest.

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PALLIATIVE CARE

1386O Cancer cachexia (CAX), anorexia and muscle wasting (sarcopenia) assessment in non-small cell lung cancer (NSCLC): an observational study in 531 patients

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Background: Since publications highlighting the role of sarcopenia, weight loss (WL) is no longer the corner stone of malnutrition assessment. An international consensus proposed in 2011 a definition and a staging of CAX, mainly based on WL, sarcopenia, inflammation and anorexia (Fearon). We initiated this study to fill the gap of epidemiological data on CAX in NSCLC in France and Belgium.

Methods: This cross-sectional, prospective, multicentric study was conducted in Patients (pts) with NSCLC regardless of the tumor stage and the treatment line. Skeletal muscle mass (SMM) was assessed by analyzing L3 CT-scan image. Pts completed Anorexia/CAX subscale of FAACT and EORTC QLQ-C30 health related quality of life (QoL) questionnaires. Primary endpoint was the frequency of CAX according to Fearon criteria. Secondary endpoints were the frequency and the characteristics of the other stages of CAX focusing on early and discrete malnutrition changes (pre-CAX).

Results: 539 NSCLC pts were recruited within 3 months in 2016 by 56 sites, analysis population was of 531 pts and 312 had SMM assessment. Median age was 66 years, 66.5% were males, 79.9% were PS < 2, and the tumor stage was mainly IIIB-IV (87.3%). 38.7% of pts had CAX, 33.8% pre-CAX and 0.9% refractory CAX. CAX was associated with molecular tumor profiles: 23.9% in patients EGFR, ALK, ROS1, BRAF or HER2 positive, 41.4% in K-RAS+ and 43.2% with no molecular abnormality ($p = 0.003$). Interestingly, the more advanced the CAX stage is, the poorer the score of functional scale (except cognitive) of the QoL questionnaire ($p < 0.0001$). Sarcopenia was present in 66.7% of CAX pts and 68.5% of pre-CAX pts (all without WL or WL $\leq 2\%$). Notably, 25.8% of pre-CAX pts had only sarcopenia with limited WL ($\leq 2\%$) and no anorexia (questioning the mechanisms of sarcopenia). In pts with limited WL ($\leq 2\%$), the loss of appetite was associated with sarcopenia in 44% of the cases.

Conclusions: This is the first study showing an association between molecular abnormality in NSCLC and cachexia. It has also shown that it may be useful to detect sarcopenia in pts with limited WL ($< 2\%$), especially in those with loss of appetite. Cachexia stages were associated to functional QoL items.

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Legal entity responsible for the study: Chugai Pharma France

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1387PD Prevalence and recent time trend in aggressiveness of cancer care near the end of life: an expanded assessment in a cohort study

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Background: There is growing concern in society about aggressiveness of cancer care near the end of life (ACCEoL), mainly in metastatic disease. This study aims to determine prevalence and recent time trend of ACCEoL of adult cancer patients in a European country, comparing metastatic with others.

Methods: Cohort study of adults with ICD-9-CM diagnosis of cancer, who died in public hospitals in mainland Portugal (Jan'10 - Dec'15), identified from the Hospital Morbidity database (HMD). HMD provided data on primary cancer site, presence of metastatic disease and primary outcome: a composite ACCEoL indicator aggregating presence of 1 of 14 individual indicators in the last 30 days of life or chemo, immunotherapy or biological agents in the last 14 days of life (expansion of Earle et al 2004 framework). We calculated the prevalence of composite and individual indicators and examined time trends (chi2 test for trend) for the whole cohort, in metastatic disease and for main primary cancers. We considered clinically meaningful $> 5\%$ change.

Results: 92,155 patients were included (median age 73 yo, IQR 62-81; 61.9% male; 53.0% metastatic). The prevalence of the ACCEoL was 71.1%, 69.9% in metastatic patients vs. 72.6% in others ($p < 0.001$), and varying by primary cancer from 62.7% in breast to 79.3% in haematological ($p < 0.001$). The most prevalent individual indicators were > 14 days in hospital (42.7%; 42.3% in metastatic) and surgery (27.8%; 26.4% metastatic). The least prevalent were permanent tracheostomy (0.1%) and percutaneous gastrostomy (0.3%). Primary outcome remained stable overtime and despite some individual indicators showed statistically significant changes in study timeframe, none of these had $> 5\%$ change.

Conclusions: Surprisingly, we found unchanged trends of high ACCEoL among adult patients and no clinically meaningful difference for metastatic disease group. A lack of integrated palliative care, even with growing resources in the timeframe analysed, suggest that these have not been enough to reduce ACCEoL. The reduced ACCEoL in patients who died with slow progressive cancers (e.g. breast) suggests that better knowledge of disease trajectories can contribute towards reducing ACCEoL.

Legal entity responsible for the study: N/A

Funding: Calouste Gulbenkian Foundation, Liga Portuguesa Contra o Cancro - Núcleo Regional do Sul

Disclosure: All authors have declared no conflicts of interest.

1388PD Open-label randomized study of individualized pharmacokinetically (PK)-guided dosing versus body surface area (BSA) dosing of paclitaxel (PTX) in advanced Non-Small Cell Lung Cancer (NSCLC) NCT02058433

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Background: Variability of PTX exposure using BSA dosing is well documented and often leads to severe toxicities. While carboplatin is dosed to obtain a specific exposure, paclitaxel is conventionally dosed by BSA, leading to a wide range of exposure. This study compared PTX PK-guided dosing to BSA dosing in a PTX-carboplatin regimen treating stage IIIB/IV NSCLC. This is the final analysis of interim results presented at ASCO 2015 (Poster #375). ClinicalTrials.gov Identifier NCT02058433.

Methods: 309 patients with stage IIIB/IV NSCLC were randomized to receive up to 4 cycles of first line 3-weekly carboplatin (AUC 5) and a PTX dose of 175 mg/m^2 (Arm A), or a PTX PK-guided dose (Arm B) to achieve a time above a PTX plasma concentration of 0.05μM ($T_{c>0.05}$) for 26 to 31 hours. Response was classified according to Response Evaluation Criteria in Solid Tumors Group. PTX concentrations were

measured by immunoassay; $T_{c>0.05}$ was calculated with PK software. The primary endpoint was reduction of grade 4 hematological toxicities.

Results: There were 164 patients in Arm A and 155 patients in Arm B, with 191 males and 128 females participating. PK-guided dose adjustment resulted in doses that were widely distributed 73 – 175 mg/m^2, and statistically lower than in the BSA arm (by 24%, $p < 0.001$). Compared to Arm A, PK-guided dosing significantly reduced grade 4 neutropenia by 35% ($p = 0.002$, 23% vs. 16%) over 4 cycles. The incidence of severe (grade $\geq$3) neutropenia was also significantly reduced by 25% in Arm B over all cycles ($p = <0.001$). Additionally, neuropathy ($\geq$ grade 2) was reduced from 20% in Arm A to 8% in Arm B ($p = 0.008$), representing a 60% reduction over all cycles. Response rates were not significantly different; objective response rates were 23% in Arm A and 29% in Arm B ($p = 0.285$); stable disease rates were 49% in Arm A and 42% in Arm B ($p = 0.0.240$).

Conclusions: Results of this study are in agreement with a previous report, and present further evidence that PK-guided dosing reduces severe toxicities. This is accomplished by an overall lowering of dose intensity, while still maintaining efficacy. PK-guided dosing personalizes chemotherapy, and may be useful in patient management.

Clinical trial identification: 02058433.

Legal entity responsible for the study: Tonji University Affiliated Shanghai Pulmonary Hospital, Tongji University

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1389PD Prognostic impact of drug interactions in patients with advanced cancer

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Background: The risk of drug-drug interactions (DDI) increases with the number of comedications. The prognostic impact of DDI in oncology is poorly understood.

Methods: We included 105 patients with advanced NSCLC, 100 patients with advanced ER-negative breast cancer (BC) and 100 hospice inpatients (HO) with advanced malignancies between 2010 and 2015. Data collected included all anticancer and non-anticancer drugs received, age, gender, presence of CNS metastases, smoking status, ECOG performance status (PS), Charlson comorbidity score and overall survival (OS) from the time of incurable cancer. Potential DDI were assessed using the hospINDEX of all drugs approved in Switzerland in combination with the DDI software - flycicle mode (HCI Solutions, Bern, Switzerland). Primary study objective was to assess the prognostic value of the severity of DDI per patient cohort using Kaplan-Meier statistics, uni- and multivariate Cox regression models. The study had a power of 84% to detect a survival difference of 25%.

Results: The median number of drugs was 5 (range 0 to 15) in all patients, lowest in BC (4) and highest in HO (6). A major risk for DDI was detected in 74 patients (24.3%) overall, including 29 NSCLC patients (27.6%), 25 BC patients (25.0%) and 20 HO patients (20%). The number of drugs was significantly associated with the risk of DDI ($p < 0.0001$). The risk of a major DDI increased from 14% in patients with <4 drugs to 24% in patients with 4-7 drugs, 40% with 8-11 drugs and 67% in patients with >11 drugs. Median OS was 8.6 months in NSCLC, 33 months in BC and 1.2 months in HO. The severity of DDI was significantly associated with inferior OS in BC (HR = 1.34, $P = 0.018$), but not in NSCLC or HO. The severity of DDI remained significantly associated with OS in BC (HR = 1.34, $P = 0.017$) after correcting for patient age and ECOG PS.

Conclusions: Severity of DDI is a significant and clinically relevant prognostic factor in advanced BC patients. Prospective trials should evaluate the potential benefit of avoiding polypharmacy in this group of patients. In the meantime, increased caution with polypharmacy seems warranted when treating patients with advanced cancer.

Clinical trial identification: 2016-00283 (BASEC, national trial identifier)

Legal entity responsible for the study: Markus Joerger MD-PhD ClinPharm

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1390P Efficacy of anamorelin in advanced non-small cell lung cancer (NSCLC) patients with anorexia/cachexia and modified Glasgow Prognostic Score (mGPS) of 2: Pooled analysis of two phase 3 trials

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Background: Anorexia/cachexia occurs in patients with advanced NSCLC. In 2 randomized, double-blind, placebo-controlled phase 3 trials in cachectic NSCLC patients, the ghrelin receptor agonist anamorelin was well tolerated and significantly improved body composition parameters and anorexia/cachexia symptoms over 12 weeks (Temel JS et al, *Lancet Oncol* 2016). The mGPS (0–2) has independent prognostic value; patients with mGPS 2 have worse prognosis. This analysis determined anamorelin's efficacy in cachectic NSCLC patients with mGPS 2 (C-reactive protein levels >10mg/L and albumin levels <3.5g/dL).

Methods: Stage III/IV NSCLC patients with cachexia (BMI<20 kg/m^2 or $\geq$ 5% weight loss during prior 6 months) were randomized 2:1 to once-daily oral anamorelin 100 mg or placebo up to 12 weeks. An ad-hoc efficacy analysis was performed in the modified intent-to-treat population (N = 829) to assess whether mGPS score at baseline may predict differences in anamorelin treatment effect size at end of study (or last observation carried forward since week 6 or 9).

Results: Anamorelin treatment effect was statistically significantly better, compared with placebo, for all body composition parameters in all mGPS subgroups. This effect was numerically larger in patients with mGPS 2 and statistically significant, compared with placebo, for all analyzed parameters, except fatigue subscale score (Table). In patients with mGPS 2, the placebo-adjusted mean increase in body weight exceeded the 5% weight loss cutoff used as an official criterion for cancer cachexia diagnosis.

Table: 1390P

	Treatment Effect of Anamorelin in patients with mGPS 2 (n = 123)		
	Mean	95% CI	*P* value, compared with placebo
Body weight, kg	3.07	1.47–4.68	<0.001
Body weight change, %	5.40	2.82–7.97	<0.001
Lean body mass, kg	1.84	0.62–3.06	0.003
Appendicular lean body mass, kg	1.04	0.32–1.77	0.005
Fat mass, kg	1.35	0.38–2.31	0.007
Handgrip strength, kg	2.44	0.35–4.52	0.022
FAACT Anorexia/Cachexia subscale score	5.23	1.55–8.90	0.006
Fatigue subscale score	0.67	−3.24–4.58	0.736

CI, confidence interval; FAACT, Functional Assessment of Anorexia/Cachexia Therapy.

Conclusions: In cachectic NSCLC patients with mGPS 2, anamorelin leads to significant improvements in body composition parameters and symptom burden. The extent of weight improvement in this population suggests that treatment with anamorelin may on average reverse pathologic weight loss.

Clinical trial identification: ROMANA 1: NCT01387269 ROMANA 2: NCT01387282

Legal entity responsible for the study: Helsinn

Funding: Helsinn

Disclosure: S. Kaasa: Stock ownership: Eir solutions AS. B. Laird: Advisory board membership: Chugai Pharma. R. Skipworth: Corporate-sponsored research: Research grant/agreement with Novartis. D. Currow: Unpaid advisory board member for Helsinn. Paid consultant and receive payment for intellectual property with Mayne Pharma and consultant with Specialist Therapeutics Australia Pty. Ltd. R. Giorgino: Helsin Healthcare employee. All other authors have declared no conflicts of interest.

1391P Prognostic Nutritional Index (PNI) for cost effective utilisation of newer, expensive radiation technology for palliative treatment of all cancer patients with limited life expectancy

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Background: Novel, complex, resource intensive, radiation technology is increasingly used for palliative therapy even though they are not cost effective in poor prognosis pts. (Kim IJROBP 2015;556). Since nearly half of all radiotherapy (RT) activity is palliative (Hoskin Cl Onc 2013;531), objective, validated prognostic tools are urgently needed to guide cost effective utilisation of RT. As advanced cancer is associated with poor nutritional status and immune dysfunction, we assessed prognostic role of PNI-which is based on serum albumin & peripheral blood lymphocytes.

Methods: Mortality of 233 unselected cancer pts treated over a 3 month at Nottingham was assessed. All tumour sites & histology were included. Overall Median age 68 yrs. Sites of RT field: Chest=29% Vertebrae=26% Pelvis=20% Brain=12% Limbs=6% Abd=3% Miscell=3%. 95% completed RT as planned. 93% had stage 4 cancer. PNI available for 131 pts. Majority not suitable for systemic therapy following palliative RT; only 15% and 28% had further hormones and chemo respectively.

Results: Overall Median survival was 5.82 months; 38% died within 90 days of completing RT; Pts with low PNI (<38) had statistically significant higher 30 day and 90-day mortality (table). On Cox regression, low PNI was strongly predictive of poor survival, (p 0.01; Exp(B) 0.538; [95.0% CI for Exp(B) 0.336 to 0.862]. Pts who received systemic therapy following palliative RT had better survival. (Hormones and chemo P values <0.005 & <0.001 respectively). By contrast, total RT dose, and number of RT fractions were not predictive of survival (p values 0.213 and 0.379 respectively). No survival advantage for multifraction over single fraction RT.

Conclusions: For terminally ill cancer patients, who are not fit for further systemic therapy and whose PNI is < 38, Single fraction RT should be the standard of care.

Table: 1391P

	PNI		
	<38	>38	P value
Median Age -Yrs	68	66	0.26*
Median RT dose- Gy	20	20	0.21#
Median No RT fractions	5	5	0.37
30 day mortality	10%	4%	0.05
90 day mortality	25%	15%	0.03
Median Survival	3.21 mths	10.45 mths	<0.001@

*T test;
Mann-Whitney;
Pearson Chi-Square;
@Log rank.

Legal entity responsible for the study: S Sundar
Funding: None
Disclosure: All authors have declared no conflicts of interest.

1392P Characterization of cachectic patients with non-small cell lung cancer (NSCLC) according to their modified Glasgow Prognostic Score (mGPS)

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Background: Patients with advanced NSCLC often develop anorexia/cachexia, a comorbidity characterized by decreased body weight or low body mass index (BMI), which negatively impacts quality of life and life expectancy. Weight loss and BMI were suggested to have independent prognostic value (Martin L et al, *JCO* 2015). The mGPS (0–2) has independent prognostic value, where patients with mGPS 2 (C-reactive protein levels >10mg/L and albumin levels <3.5g/dL) have worse prognosis. Here, we investigated the characteristics of NSCLC patients with cachexia according to their mGPS, and whether mGPS can be used to differentiate patients with cachexia.

Methods: Patients with unresectable stage III/IV NSCLC and cachexia (BMI<20 kg/m^2 or ≥ 5% weight loss during prior 6 months) were enrolled in two phase 3 studies of the ghrelin receptor agonist anamorelin (ROMANA 1 and ROMANA 2). A pooled post-hoc data analysis was performed in the modified intent-to-treat population (N = 829), irrespective of treatment arm, to investigate the baseline characteristics of patients with mGPS 0–2.

Results: At baseline, 36% patients had mGPS 0 (n = 296), 49% mGPS 1 (n = 396) and 15% mGPS 2 (n = 123). Patients who lost <10% body weight during the prior 6 months had mainly mGPS 0–1; in contrast, among patients who lost >10% body weight, a higher percentage had mGPS 2. Patients with mGPS 2 had on average substantially lower values of body weight, body composition parameters, handgrip strength and anorexia/cachexia and fatigue scores than the other mGPS subgroups (Table).

Conclusions: While patients with cachexia present mGPS scores that vary from 0–2, a higher percentage of patients with mGPS 2 was observed among those with >10% body weight loss. The baseline characteristics observed in patients with mGPS 2 are worse than in the other mGPS subgroups, suggesting that mGPS may be helpful in identifying patients with more-advanced cachexia.

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Legal entity responsible for the study: Helsinn
Funding: Helsinn
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Table: 1392P

	Baseline characteristics based on mGPS score		
	mGPS 0 (n = 296)	mGPS 1 (n = 396)	mGPS 2 (n = 123)
Body weight loss, n (%) ≤ 10% > 10%	205 (43.0) 92 (27.1)	218 (45.7) 178 (52.5)	54 (11.3) 69 (20.4)
Mean body weight, kg (SD)	66.9 (13.66)	67.4 (12.73)	63.0 (13.77)
Mean lean body mass, kg (SD)	44.9 (8.64)	46.2 (7.78)	44.5 (8.54)
Mean appendicular lean body mass, kg (SD)	19.3 (4.59)	19.7 (3.95)	18.4 (4.25)
Mean fat mass, kg (SD)	19.4 (8.06)	19.0 (7.80)	16.3 (8.01)
Mean handgrip strength, kg (SD)	32.2 (11.74)	32.7 (10.92)	27.2 (9.91)
Mean FAACT Anorexia/Cachexia subscale score (SD)	31.6 (7.92)	29.5 (8.16)	25.5 (8.77)
Mean fatigue subscale score (SD)	32.4 (9.74)	30.6 (10.21)	25.4 (10.95)

FAACT, Functional Assessment of Anorexia/Cachexia Therapy; mGPS, modified Glasgow prognostic score; SD, standard deviation.

1393P Chemotherapy in advanced cancer patients with poor performance status (PS) initiated in an integrated oncology and palliative care (PC) setting: an observational comparative study

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Background: Advanced cancer patients (ACP) with poor PS often get systemic anticancer treatment (SAT). A combined PC and medical oncology structured approach involving double boarded palliative oncologists (PallOnc) is investigated.

Methods: Medical chart review over 2½ years, with locally developed (adapted from Blum D JPSM 2014) tool, of all ACP PS > 1 in a tertiary PC unit (330 pts/year, death rate 40%, length of stay [LOS] 12 days) receiving intravenous SAT (pharmacy orders). ACP with new initiated SAT were compared with continued SAT for tumor history, PS, and outcomes; in new SAT the PallOnc processes decisional process, Palliative Interventions (PIs), and primary dose reduction were analysed.

Results: Of 95 ACP receiving SAT 65 (68%) were PS > 1. In 36 ACP a new SAT was initiated, in 29 continued. Comparable were age (years, mean: 65 vs 63), gender (% female: 39 vs 43), PS (PS3/4: 64% vs 65%)), time since diagnosis of stage 4 (months, mean: 16 vs 14), number of anticancer treatment lines (mean: 2 vs 2) and LOS (days, mean: 26 vs 24). New vs continued SAT differed for tumors not responding (never PR or SD) to last chemotherapy (55% [7 PS2, 4 PS3] vs 27% [1 PS2, 2 PS3], monotherapies (67% vs 45%), death at PC unit (14% vs 41%), overall survival (1 patient alive, 1 lost-to-follow-up; days, median: 83 vs 58, mean 152 vs 128), PS at demission compared to admission (stable PS: 33% vs 24%; improved PS: 50% vs 24%), and ACP who died ≤14 days after last SAT (22% vs 14%). No G3/4 non-hematological toxicity was reported. In the new SAT group the decisional process took 11 days (median, range 0-48), explicit goals of SAT were documented in 81% (44% specific tumour-related symptoms), attitude towards SAT in 86% ACP (unwilling, ambiguous 4/31, wants, imperative 17) and 42% physicians (0, 15). Of 5 PIs Illness understanding, symptom control, end-of-life preparation, network & family support, spiritual needs) all were delivered in 21 ACP (58%), 4 and 3 in 7, 2 in 1. Primary dose reduction was applied in 2/4 PS4 patients (1: 5-25%,1: 26-50%), 13/19 PS3 (5, 8) and 11/13 PS2 (7, 4) ACP.

Conclusions: In a setting with PallOnc anticancer treatment in poor PS patients seems feasible. The encouraging data may foster prospective research.

Legal entity responsible for the study: Cantonal Hospital St.Gallen, Switzerland

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1394P Previous palliative care encounter is associated with lower total hospital charge and shorter length of stay in patients with metastatic cancer

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Background: Patients with metastatic cancer require substantial heath care resources. Palliative care has been increasingly recognized for improvement of quality of life and reducing healthcare costs. Here, we examined the effect of prior palliative care encounters on the total hospital charges (TOTCHG) and length of stay (LOS) during the subsequent hospitalization.

Methods: We used National Inpatient Sample (NIS) 2014 to extract data for patients non-electively hospitalized with corresponding ICD9 code of previous palliative care visit (ICD9 code V667) and metastatic cancer. NIS is a nationally representative survey of hospitalizations conducted by Heathcare Cost and Utilization project. It represents 20% of all hospital data in the US. Univariate regression screening (threshold P > 0.1) and hybrid selection were used to create multivariate regression models. Relationship between TOTCHG and previous palliative care encounter as well as LOS and previous palliative care encounter were analyzed by using established models.

Results: A total number of 136591 patients admitted non-electively with metastatic cancer was identified among which 24736 had been coded for previous palliative care encounter. Teaching hospital admission, rural hospital admission, self-pay, increased age and increased Charlson score were associated with higher rate of previous palliative encounter. The multivariate regression model for LOS and previous palliative care visit were adjusted for survival outcome, number of procedures during hospitalization, number of previous chronic conditions, and number of the diagnosis during hospitalization. The model for TOTCHG and previous palliative care visit were adjusted for survival outcome, number of procedures and length of stay. We found that previous palliative care encounter was associated with both lower total hospital charge (P < 0.0001) and shorter length of stay in patients with metastatic cancer (P < 0.0001).

Conclusions: Prior palliative care visit has been associated with decreased length of stay and total hospital charges. Future studies are needed to determine if early outpatient palliative care encounter will especially benefit patients with certain tumor types.

Legal entity responsible for the study: Yuzhou Liu

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1395P Specialized ambulatory palliative care: (SAPV) 5-year results of a multi-professional care model by HomeCare linker Niederrhein gGmbH (HC) in the Lower Rhine region

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Background: In recent times, German legislation has given terminally ill patients the right to receive SAPV, a multi-professional palliative care model which is aimed at prevention of hospital admission and enabling patients to die at home despite severe symptoms and a high need for palliative care. This new type of care raises the question about the best implementation and impact of SAPV. HC provides SAPV to 560.000 inhabitants of the city of Mönchengladbach and the district of Viersen.

Methods: Data collected during daily care from 2012 to 2016 are summarized and analysed in order to describe the implementation and results of SAPV.

Results: 1798 patients were treated in 5 years. The first contact with SAPV was initiated by a GP in 30% of patients and by a specialist in 4.5%; in 26% through a hospital, in 6% by a palliative care unit and in at least 30% by non-medical participants, such as relatives, nursing services, counseling centers etc. 20% of all patients were treated only temporarily by SAPV. 6% were admitted to a hospice, 14% were transferred to regular care after counseling or crisis intervention. Of the remaining patients, only 3.3% had to be hospitalized at the end and 96.7% were able to remain in their chosen home environment. That was at home for 80%, at a relative's home for 3%, in a nursing home for 14%, and miscellaneous for the remaining 3% of patients. Sonography, thoracic and abdominal paracentesis, patient-controlled analgesia etc. were performed in the patient's home by the SAPV team. Of all 1798 patients, 112 had to be hospitalized; 64 were subsequently retreated with SAPV and 48 were not. The main reasons for hospitalization were palliative interventions due to ileus and urinary retention in the upper tract, radiation of a fracture, psychosocial decompensation of the supporting relatives and confirmation of the palliative concept. The average treatment duration was 19 days, the median was under 10 days. In detail, 112 patients were treated for less than 24 hours, 271 patients for less than 48 hours, 57 patients were treated for more than 90 days and 4 patients for over 200 days.

Conclusions: The wish of patients to die at home and to avoid unnecessary hospitalization can be achieved with this model of specialized care. Further comparative investigations are necessary to identify the optimal implementation and impact of SAPV.

Legal entity responsible for the study: Ulrich Grabenhorst

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1396P Increasing palliative interventions at the end of life: patterns in metastatic colorectal cancer (mCRC)

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Background: Advances in chemotherapy for mCRC have improved median survival to more than 24 months. This has resulted in increased opportunity to undergo more frequent interventions for symptom relief at the end of life. We explored patterns of palliative interventions (surgery, endoscopy, interventional radiology (IR), drainage procedures, radiotherapy) in mCRC patients over a time of evolving chemotherapy regimens.

Methods: A retrospective review was undertaken of all mCRC patients referred to palliative care at a tertiary cancer center in Toronto, Canada. Patients treated 2000-2004 (early cohort) were compared to 2006-2010 (later cohort) as more effective palliative chemotherapy was available in the later time period. Descriptive statistics, t-tests, and chi-squared tests were employed.

Results: A total of 542 (212 early and 330 later cohort) patients were included. Compared to the early cohort, the later cohort was significantly younger (62 vs 65 years, p = 0.012), had more Stage 4 disease (47 vs 42%, p = 0.029), fewer curative surgeries (58 vs 70%, p = 0.005) and fewer had adjuvant chemotherapy (26 vs 38%, p = 0.002). Palliative care referral was delayed for the later cohort with longer times between diagnosis of unresectability and referral (13 vs 8 mths, p = 0.0019) and shorter times between referral and death (6 vs 8 mths, p = 0.019). More patients in the later cohort had palliative surgery (31 vs 22%, p = 0.015), palliative IR procedures (15 vs 4%, p < 0.0001) and did not receive any chemotherapy (44 vs 29%, p < 0.0001). The later cohort underwent more interventions in the last months of life with more chemotherapy and drainage procedures closer to death (7 vs 12 mths, p = 0.002 and 2 vs 9 mths, p = 0.006 respectively). There was no difference in survival (calculated from date of diagnosis to death) between the cohorts (median survival 35 months).

Conclusions: In their final months of life, palliative mCRC patients are undergoing more interventions requiring multi-disciplinary input with the aim of improving quality of life than previously. Increasing use of interventions in the last months of life has significant ramifications for patients, service provision, staffing and funding.

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Disclosure: All authors have declared no conflicts of interest.

1397P Chronic pleural effusion in malignancy: A single center's ten years expertise with indwelling pleural catheters

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Background: Chronic and recurrent pleural effusion (PE) in malignant diseases is a common cause of dyspnea, cough and chest pain. The vast majority is malignant pleural effusion (MPE), nevertheless disease-associated but not directly disease-caused paramalignant pleural effusions (PPE) have also been described. Talc pleurodesis had been the only treatment option for decades, while for 20 years indwelling pleural catheters (IPC) have emerged as an alternative leading to spontaneous pleurodesis without any chemical agent in 40-50%.

Methods: Our aim is to explore patient characteristics, procedural variables and outcomes in a large population of patients with IPC due to PE in malignancy. Further, our objective is to identify factors associated with outcome.

Results: From 2006 until 2016 448 IPC were inserted in 395 patients, 52 received bilateral drainages (12.7%). 77.0% of the effusions were malignant (n = 304), 14.9% paramalignant (n = 59), in 8.1% the etiology could not be clarified (n = 32). The most common underlying diseases were ovarian cancer (30.6%, 121 patients), lung cancer (23.0%, 91 patients) and breast cancer (11.4%, 45 patients). The median length of insertion was 1.2 months (0.03-23.6), the median survival time after insertion 2.4 months (lung cancer 1.6 months, ovarian cancer 2.8 months, breast cancer 4.0 months). Spontaneous pleurodesis was observed in 28.6% (128/448 catheters) and was significantly associated with overall survival (HR 0.54, 95%-CI 0.39-0.75, $p < 0.001$). Complications occurred in 12.3% of all procedures (55/448 catheters), in 6.5% the catheter had to be removed (29/448 catheters). The most common complications were superficial infections (n = 14), empyema (n = 11; 1 grade 5 complication) and mechanical obstruction of the catheter (n = 13).

Conclusions: In conclusion, our retrospective series is the largest to date to report on IPC in malignancy and showed a manageable safety profile. Spontaneous pleurodesis was significantly associated with survival.

Legal entity responsible for the study: Charité Universitätsmedizin Berlin

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1398P Aggressiveness of care at the end of life in children with cancer: A nationwide cohort study

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Background: Cancer remains the leading medical cause of death in children. Ensuring quality of life should be a priority, but it may be difficult to stop treatments, particularly in settings where palliative care is scarce. Little is known about how many children dying from cancer experience aggressive care near the end of life (ACCEoL) in such settings (the most common worldwide). Our study aims to determine time trends in the prevalence of ACCEoL in this population.

Methods: Cohort study of children (0-17yo) who died with ICD-9-CM diagnosis of cancer in public hospitals in mainland Portugal (Jan'10 to Dec'15), identified from the Hospital Morbidity database. Based on previous studies and clinical experience, measures of ACCEoL comprised: in last 14 days of life: a) intravenous chemo/immunotherapy; in last 30 days of life: b) >14 days spent in hospital, c) >1 hospitalization, d) intensive care unit (ICU) admission, e) advanced life support (e.g. cardiopulmonary resuscitation), f) insertion of devices (e.g. central vascular access, CVA), g) total parenteral nutrition (TPN). We calculated prevalences and tested for time trends using chi2 for trend.

Results: The study included 300 patients (median age 9 yo, IQR 4-14, 58.7% male). The prevalence of ACCEoL was stable over time, with 87.8% of the children experiencing at least one ACCEoL measure (85.2% in 2010, 88.4% in 2015; $p = 0.816$)). The most prevalent individual ACCEoL measures were >14 days spent in hospital (51.0%) and >1 hospitalization (43.3%). Most measures showed no statistically significant time trend.

Conclusions: In a setting in early stages of pediatric palliative care development, we found that eight in ten children dying from cancer experience ACcEoL in their last month of life. This estimate is higher than those found in countries in more advanced developmental stages and may indicate a need to increase paediatric palliative care availability. The findings also prompt healthcare professionals to reflect on their current practice, balancing treatments and hospitalisations with patients' quality of life in the days they have to live.

Legal entity responsible for the study: N/A

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PREVENTION AND SCREENING

1401PD Fluctuating cancer screening uptake in France: results of the 5th EDIFICE survey

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Background: The EDIFICE nationwide surveys assess attitudes to cancer screening in France. All 5 self-reported surveys (2005, 2008, 2011, 2014 and 2016) focused on breast (BC), colorectal (CRC), prostate cancer (PC) screening; the 4th and 5th editions also included cervical (CC) and lung cancer (LC) screening.

Methods: The 5th survey recruited a representative sample of 1299 subjects (men [M], women [F]; age, 50-74 y; no history of cancer) and focused on target populations of the national screening programs for BC and CRC (50-74 y), and on specific subpopulations for PC (M, 50-75 y), CC (F, 50-65 y) and LC (M and F, 55-74 y) screening. Participants were questioned about uptake of at least 1 lifetime screening test and compliance to recommended intervals. Data analysis encompassed nationwide screening programs, opportunistic screening, and vulnerability (assessed by the EPICES score).

Results: Rates for at least 1 lifetime BC screening test (screening rate) were 93%/94%/95%/97%/97% in 2005/2008/2011/2014/2016, respectively. In line with recommendations, 75%/83%/83%/81%/75% women reported having had a mammogram in the past 2 years (compliance), with a significant drop in 2016 *vs* 2014 (P=0.02). Vulnerability had a negative impact on compliance in 2016, though not previously. For CRC, screening rates were 25%/38%/59%/60%/64%. Compliance (FOBT or FIT in the past 2 years) increased steadily from 7% (2005) to 33% (2014), and rose significantly to 38% in 2016 (P=0.02). The rise was mainly observed in the 50-54 y age group, among men, and in non-vulnerable subjects. In 2016, a significant drop in overall CC screening uptake was observed (99% in 2014 vs 94% in 2016, P<0.01), particularly among unemployed women (98% in 2014 vs 92% in 2016; P=0.03). Figures for at least 1 lifetime PC screening test were 36%/49%/50%/49%/42%, with the 2016 survey showing a significant decline, notably among unemployed (P=0.02) and non-vulnerable populations (P=0.05). LC screening rates (M,F) remained stable between 2014 and 2016.

Conclusions: In 2016, compliance to national programs was seen to be high for BC screening (despite a decline), and on the rise for CRC, possibly due to the use since 2015 of the new FIT test. Although a national program is due to be implemented in France, uptake of CC screening is on the decline.

Legal entity responsible for the study: Kantar Health

Funding: Roche France

Disclosure: S. Couraud, L. Greillier, J-Y. Blay, A. Cortot, J-F. Morere, F. Eisinger: Received honorarium fees from Roche/Edifice surveys were funded by Roche S.A. C. Lhomel: Employee of Roche. All other authors have declared no conflicts of interest.

1403P Community-based lung cancer screening of high-risk population with low-dose computed tomography in China

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Background: Low-dose computed tomography (LDCT) screening for lung cancer has been recommended for high-risk individuals meeting the National Lung Screening Trial (NLST) criteria. However, there still is a debate concerning respective recommendations for Asian countries. Meanwhile, the proper duration and interval for lung cancer screening remains uncertain.

Methods: From November 2013 to July 2016, participants from Xuhui district of Shanghai were aged 45-70 years, and with either of the following risk factors: 1) smoking history ≥20 pack-years, and, if a former smoker, had quit within the past 15 years; 2) cancer history in immediate family members; 3) personal cancer history; 4) professional exposure to carcinogens; 5) long term exposure to second-hand smoke; 6) long term exposure to cooking oil fumes. The eligible participants were randomly assigned to a screening arm with two rounds of alternate years LDCT screens and a control arm.

Results: A total of 6659 eligible participants were enrolled, 3147 participants were randomly assigned to control arm, 3512 were assigned to LDCT prevalence screening (S1), of which 1516 participants underwent the second round of LDCT screening (S2) in the alternate year. Positive screening results were observed in 849(24.2%) participants in S1 and 380 (28.0%) in S2. 80 (2.3%) cases were highly suspected of lung cancer in S1 and 31 (2.0%) in S2 according to the suggestions from multiple disciplinary team. By April 2017, lung cancer was diagnosed in 44 participants (1.3%) after S1, 12 (0.8%) after S2, and 10 (0.3%) in the control group (stage 0 to I: 97.7%, 91.7% vs 20%; stage II to IV: 2.3%, 8.3% vs 80%). Only 18 (32%) of these 56 lung cancer patients detected by LDCT would have qualified as NLST high-risk patients. There were 2 lung cancer-specific deaths in control group, whereas 0 in the screening arm participants.

Conclusions: LDCT screening increased the detection of early-stage lung cancer and reduced lung cancer-specific mortality. In China, lung cancer CT screening may also benefit patients outside the NLST criteria with great efficiency. Screening done at biennial intervals could be taken into consideration due to few advanced-stage diseases.

Legal entity responsible for the study: Shanghai Chest Hospital

Funding: Shanghai Municipal Commission of Health and Family Planning

Disclosure: All authors have declared no conflicts of interest.

1404P Colon cancer screening by fecal immunochemical testing in Iran

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Background: Colorectal cancer (CRC) is the third-most common cancer in Iran. We aimed to measure the uptake and feasibility of a pilot CRC screening programme based on fecal immunochemical test (FIT) in population aged between 45 and 75 years and the implications for scaling-up at the national level.

Methods: This pilot study was conducted in Tehran and individuals aged between 45 and 75 years in rural and urban areas were enrolled in the screening programme. The FIT was offered by health navigators in primary health centers by collecting one single sample directly in to buffer kits by each participant. Health navigators aimed at increasing uptake and handled the whole screening programme from invitation to the referrals and provided the participants with information regarding the nature and importance of the CRC screening and details as to how to collect stool samples and send them back to the laboratory for analysis. If the first kit was not returned within 48 hours, a reminder call was sent. Those participants who had a positive FIT were referred to undergo a colonoscopy.

Results: A total of 1044 asymptomatic average-risk individuals were enrolled. The age mean was 54.1 and nearly 63.0% (n = 657) were female. Only small fraction of participants had awareness about CRC (13.7%) or polyps (8.3%) or screening tests (9.2%). Likewise their prior screening practice was extremely weak (2.2%). In multivariate regression analysis, awareness about CRC and screening tests significantly varied according to the ethnic groups, years of schooling, and family history of cancers ($P < 0.05$). In sum, 1002 returned the FIT kit, of which stool sample in six participants (0.6%) was deemed unsatisfactory for testing. The FIT uptake was 96.0%, the positivity rate was 9.1% and the detection rates were 11.9% for adenomas and 7.1% for advanced adenomas. No cancer was detected.

Conclusions: This is the first study on minimal quality metrics within a CRC screening process for the pilot phase and indicates that FIT modality as a test of choice is a safe and highly acceptable method of CRC screening in average-risk asymptomatic people. We suggest FIT as an initial CRC screening tool along with other preventive services in primary health care system in the nation.

Legal entity responsible for the study: Prof. Reza Malekzadeh

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1405P Diagnostic analysis of patients referred from general practitioner with serious non-organ-specific symptoms and signs of cancer: A retrospective cohort study

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Background: Recently, a diagnostic fast track for patients with serious non-organ-specific symptoms and signs of cancer was established in Denmark. For patients without cancer diagnosed within the first month, the prognosis is currently unclear.

Methods: A retrospective cohort study of 926 patients referred to Diagnostic Outpatient Clinic (DOC) at Herlev Hospital from April 2012 to December 2013. Baseline clinical parameters were collected from patient records. Time to cancer, death, cancer specific mortality (CSM), and death due to other causes were recorded until May, 2016. 724 patients were identified without cancer one month after examination and divided into 2 sub-cohorts based on the initial assessment: true negatives (TNs; patients diagnosed without cancer at DOC and after 1 month) and false positives (FPs; patients referred from DOC with suspicion of cancer, but without cancer the 1. month). Cumulative incidence of cancer, death, CSM, and death from other causes were estimated by the Aalen-Johansen estimator using 31 days after initial assessment as baseline. Hazard radios (HR) and 95% confidence intervals (CIs) for the initial evaluation were estimated in Cox models with cancer and mortality, respectively, as outcomes.

Results: Clinical characteristics of the 724 patients: median age 65 years (range 17-92); 44% were men; 70% were referred from their general practitioner; 43% were former/current smokers; 18% were former/current alcohol abusers. The median age ($p < 0.01$) and comorbidity score ($p < 0.01$) were highest among the FPs. TNs vs. FPs had a lower risk of subsequent cancer (HR: 0.08; 95% CI: 0.05-0.13; $p < 0.01$), mortality (HR: 0.26; 95% CI: 0.16-0.41; $p < 0.01$) and CSM (HR: 0.07; 95% CI: 0.03-0.16; $p < 0.01$). Mortality from other causes was similar in the two groups (HR: 0.58; 95% CI: 0.29-1.19; $p = 0.14$). The negative predictive value (NPV) was 0.94 and the positive predictive value was 0.46. However, around 40% of the FPs was diagnosed with cancer within the first year.

Conclusions: Ruling out cancer by investigation at DOC was associated with low risk of subsequent cancer and the NPV was high. The FPs had higher risk of cancer, mortality, and CSM compared to the TNs.

Legal entity responsible for the study: Claus Larsen Feltoft

Funding: Department of Internal Medicine, Herlev and Gentofte Hospital (no specific grant number); Danish Cancer Society (grant number: R152-A9695-16-S7).

Disclosure: All authors have declared no conflicts of interest.

1406P Increased mutation burden in high-risk lung tissues: Toward precision cancer risk diagnosis

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Background: Mutations are believed to accumulate in normal tissues at extremely low levels as a result of exposure to various carcinogenic factors. The degree of accumulation, namely mutation burden, is likely to be associated with cancer risk. However, owing to the limits of current detection methods for such extremely low frequency mutations, the mutation burden present in normal human lung tissues has been unclear. To overcome this limitation, we established a novel method for the quantification of extremely low frequency mutations in DNA samples. Using this method, we aimed to reveal the presence of mutation burden in normal lung tissues and its association with cancer risk.

Methods: Somatic mutations were quantified in normal lung tissues without smoking history (n = 11) ("entirely normal lung tissues":G1), normal lung tissues with smoking history (n = 11) ("smoking-exposed normal tissues":G2), and non-cancerous lung tissues of patients with lung cancer and smoking history (n = 11) ("smoking-exposed non-cancerous tissues":G3). A sequence library (15,724 bases of 291 regions of 55 cancer-related genes) was prepared by multiplex PCR using 100 DNA molecules. Libraries were sequenced using a next generation sequencer.

Results: The mutation burden in G3 ($2.7 \pm 0.8 \times 10^{-5}$ mutations/base) was significantly higher than that in G1 ($1.8 \pm 0.5 \times 10^{-5}$ mutations/base) ($p = 0.0189$). Accumulation of somatic mutations tended to be associated with increased cancer risk (OR = 3.75; 95% CI = 0.54–26.046). C>T mutations were significantly more frequent in G2 and G3 than in G1, which is in accordance with reported mutation signatures in cancer tissues [Alexandrov *et al.*, Science, 354:2016]. GCC>GTC and CCC>CTC mutations, signatures of exposure to the nitrosamines contained in tobacco smoke, were significantly enriched in G2 and G3.

Conclusions: To the best of our knowledge, this is the first study showing that mutations accumulate in high-risk lung tissues due to exposure to tobacco smoking. This will lead to a novel approach to precision cancer risk diagnosis.

Legal entity responsible for the study: Toshikazu Ushijima

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1407P Change of natural history of hereditary diffuse gastric cancer after identification of a novel CDH1 mutation

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Background: *CDH1* germline mutations are the major cause of hereditary diffuse gastric cancer (DGC). Carriers of *CDH1* mutations can present multiple signet ring cell carcinoma foci at early age. Therefore, prophylactic total gastrectomy (PTG) is widely recommended. We report a family with a novel *CHD1* mutation and analyze endoscopic and PTG findings among the mutation carriers.

Methods: Genetic *CDH1* testing by Sanger was performed in a three-generation family with multiple relatives with DGC. Direct sequencing was offered to individuals at risk >18 years. Unaffected carriers were recommended PTG and preoperative esophagogastroduodenoscopy with random gastric biopsies (RGB). Each PTG specimen was wholly sectioned (median # cassettes: 203) to look for occult cancer and histopathology was compared to RGB findings.

Results: A novel pathogenic variant in *CDH1* c.48G>A (p.Q16Q) was identified in 28 family members, 16 male/12 female. Prior to variant identification, 6 obligate carriers were diagnosed with an advanced DGC, median age 56 (53-62) years and all died of the disease. After genetic testing, 8 asymptomatic carriers were found early-stage DGC in the PTG specimen, median age 25 (19-59) years. Age-specific frequency of DGC in carriers according to PTG is shown in the Table.

Table: 1407P

	No PTG		PTG	
	n = 8		n = 20	
Age	DGC n = 6	Cumulative frequency	DGC n = 8	Cumulative frequency
10-20			1	5%
21-30			3	20%
31-40			1	25%
41-50			1	30%
51-60	5	62%	1	35%
61-70	1	75%	1	40%

Histopathological RGB and PTG correlation was performed in 17 carriers attended at our institution (May 2013-Sept 2015). Median age at PTG was 34 (19-63) years. All preoperative RGB were negative, but one, which identified a single milimetric DGC foci. PTG specimens revealed one Tis and six T1a DGC, conferring RGB a predictive negative value (PNV) of 66% for DGC. Stage IA DGC had a median of 2.8 foci/gastrectomy, localized in the body (83%) and atrium (17%), with average diameter 0.73 mm and e-cadherin expression in 100% of the foci. No severe postoperative morbidity was recorded after a median follow-up of 29 (16-44) months.

Conclusions: PTG has changed the natural disease history in c.48G>A *CDH1* carriers. Endoscopic RGB showed a low PNV for DGC and PTG is still highly recommended. More reliable screening methods are required in order to delay PTG in *CDH1*-mutation carriers.

Legal entity responsible for the study: Vall d'Hebron Hospital

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1409P Cervical cancer screening in France: recent change in behaviors

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Background: Cervical cancer (CC) is the fourth most common cancer in women in France. Human papillomavirus vaccination and screening are complementary secondary prevention measures against CC. Screening by conventional Pap smear is recommended every three years for women aged 25-65y.

Methods: The EDIFICE nationwide observational surveys assess population attitudes to cancer screening in general. Representative samples of the French population aged 50-75 years are interviewed by phone using the quota method. Although the French CC screening program covers all women aged 26-65y, the present analysis pertains to a subpopulation aged 50-65y (N = 356 in 2014 and N = 460 in 2016). Interviewees, with no personal history of cancer, were asked if they had ever had a smear test during a gynecological exam. The date of the last test was noted. Data analysis focused on age group, socioprofessional categories (SPC) and social vulnerability (defined by the EPICE score).

Results: In 2016, 94% of interviewees reported at least one lifetime smear test vs. 99% in 2014 ($P<0.01$). In line with current interval recommendations, 74% in 2016 and 75% in 2014 ($P=0.81$) had had the latest test done in the past three years. Younger age groups were significantly more likely to be compliant with the recommendations in 2014 ($P<0.01$) though not in 2016 ($P=0.18$). SPC also had a significant impact on compliance rates in 2016 ($P=0.01$) but not in 2014. Vulnerable women were less likely to be screened at least once in their lifetime; this trend was non-significant in 2014 (98% vs 100% in non-vulnerable, $P=0.14$) but significant in 2016 (89% vs. 97%, $P<0.01$). Vulnerable women were also significantly less likely to be compliant with the recommendations (64% vs 81%, $P<0.01$ in 2014; 63% vs.79%, $P=0.01$ in 2016).

Conclusions: Between 2014 and 2016, participation in CC screening decreased and compliance rates stagnated. Compliance with screening recommendations was negatively affected by the following: unemployment, low SPC or classification among vulnerable populations. Additional analysis will further investigate these findings, which highlight the need for generalized population-based screening programs and targeted actions for non-participants, as advocated earlier this year by the French National Cancer Institute (INCa).

Legal entity responsible for the study: Kantar Health

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1411P Genetic counseling, screening and risk reducing practices in patients with BRCA mutations

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Background: Worldwide practices of genetic counseling remain variable. We present genetic counseling, mammography and MRI screening & risk-reducing surgeries on patients with BRCA mutations & VUS of our BRCA mutations study (El Saghir et al, Oncologist 2015).

Methods: Chart review & phone calls for collection of information were done on 45 pts out of the 250 pts tested. IRB approval obtained. 14 pts (5.6% of total) with deleterious mutations & 31 pts (12.4% of total) with VUS were included. 7 pts had metastatic breast cancer. 4 pts were not reachable. We present results on 33 pts for whom we collected information about genetic counseling, screening, Contralateral Prophylactic Mastectomy (CPM) & Risk Reducing Salpingo-oophorectomy (RRSO).

Results: 14 pts with deleterious mutations (7 BRCA1 & 7 BRCA2 positive pts) & 19 pts with 20 VUS mutations (4 BRCA1 & 16 BRCA2; 1 pt had both BRCA1 & BRCA2) were examined. Of the 14 pts with BRCA deleterious mutations, 57.14% (8/14 pts) said they received some genetic counseling from their own oncologist and not a specialized genetic counselor. 85.71% (12/14) are undergoing regular screening mammography, 35.71% (5/14) are undergoing regular screening breast MRI. 50% (7/14) underwent CPM & 57.14% (8/14) underwent RRSO. Also, 57.14% (8/14) advised their family members, namely sisters & daughters, to undergo BRCA mutation testing. Of the 19 pts with VUS mutations, only 10.5% (2/19 pts) of the pts said they received some genetic counseling. 78.9% (15/19) are undergoing regular screening mammogram, 31.5% (6/19) are undergoing regular screening MRI breasts. 1 pt underwent CPM & 2 pts RRSO. Also, only 21.0% (4/19) advised their family members to undergo BRCA mutation testing.

Conclusions: The majority of pts with BRCA mutations continue to undergo screening mammography & breast MRI. Only 50% of pts with BRCA deleterious mutations underwent CPM & 60% RRSO, while a few pts with VUS mutations underwent CPM & RRSO. Genetic counseling is mostly done by medical oncologists. Our data supports recommendations to include genetic counseling in the training and Continuing Medical Education CME of Oncologists, and to improve patient education. More importantly, there is an urgent need for more certified professional genetic counselors in Lebanon & worldwide.

Legal entity responsible for the study: Nagi El Saghir

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1413P Gastric cancer detected after Helicobacter pylori eradication at one private screening center in Japan

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Background: *Helicobacter pylori* eradication (*Hp*-er) has become widespread in Japan since Japanese public insurance started covering that treatment.

Methods: The data of the esophagogastroduodenoscopy (EGD) screening program from June 2012 through February 2017 at Ota Memorial Hospital (OMH) in Japan was reviewed. All cases of gastric cancer (GC) with *Hp*-er history (*Hp*-er Hx) detected in the EGD screening program were analyzed to reveal their characteristics.

Results: 21,817 individuals were enrolled in EGD screening program of OMH during the above period. 5,563 of them (25.5%) have *Hp*-er Hx. Fifty cases of GC were found in that program (detection rate 0.23%) and 27 of them (54%) have *Hp*-er Hx (detection rate 0.49% in participants with *Hp*-er Hx). The intervals between *Hp*-er and GC detection were ascertained in 19 cases. Median duration is 3 years and the longest interval is 20 years. Anti-*Hp* IgG antibody (*Hp*-Ab) was measured in 26 GC cases with *Hp*-er Hx. Although 6 cases still had 10 or more than 10 U/ml (*Hp*-Ab "positive"), other 20 showed less than 10 U/ml (*Hp*-Ab "negative") and 5 of them revealed less than 3 U/ml. Seventeen cases (63%) of GC with *Hp*-er Hx were the current or former smoker. The median of their Brinkman index is 690. Other 10 cases were non-smoker and 8 of them (80%) had family history of GC although only 23.5% had such a family history among current or former smokers with *Hp*-er Hx. All 27 cases of GC with *Hp*-er Hx suffered from chronic atrophic gastritis (CAG). Twenty-five of them were diagnosed as the open type (or advanced type) CAG. Other two had the closed type CAG but C-3 (nearly advanced atrophy) in Kimura-Takemoto's CAG classification. Although GC lesions were localized at any part of the stomach, all of them were found in atrophic gastric mucosa by EGD. Five of them were diffuse type and other 22 were intestinal type on Lauren's classification in their histopathologic findings.

Conclusions: It is important for individuals with *Hp*-er Hx to take periodic or annual EGD screening to search for GC because more than half cases of GC had *Hp*-er Hx in EGD screening program of OMH. Among them, ones with smoking or family history of GC have high risk. It is necessary for such individuals to have meticulous EGD inspection of the whole stomach, especially the area of atrophic gastric mucosae.

Legal entity responsible for the study: Ota Memorial Hospital

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1415P NGS and Sanger screening for BRCA1/BRCA2, CHEK2 and TP53 in Argentinian high-risk breast/ovarian cancer families and bioinformatic studies: Initial results

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Background: In this study, we aimed at reporting the frequency of BRCA, CHEK2 and TP53 mutations in our high risk breast/ovarian cancer population, in order to determine the role of these genes testing in breast cancer risk assessment.

Methods: Total DNA of 484 unrelated cases and 180 relatives were sequence using either Sanger (564) or NGS (100) for BRCA1/BRCA2, CHEK2 and TP53 mutations. While 64.5% (312/484) of the population studied belong to jewish ethnicity, the remaining patients were european-amerindians.

Results: Of the 484 probands analyzed, 15.9% were BRCA1/BRCA2 mutation carriers, 9.7% in BRCA1, 6% in BRCA2 and one patient was double heterozygous. Overall, 18.9% of the jewish patients presented ashkenazi founder mutations and 9.9% of european-amerindian population was positive for BRCA mutations. The c.66_67delAG was the most frequent alteration, representing 34.2% of all mutations identified. Pathogenic variants in CHEK2 and TP53 genes were present in 4% and 1.1% of our european-amerindian cases. Eighteen pathogenic variants different from ashkenazi panel were identified in BRCA, three were novel and twelve not previously reported in argentinian population. Twenty-seven variants of uncertain significance were found.

Conclusions: An association between genetic ancestry and mutational profile was observed only in the Jewish population. The 66.7% of the pathogenic variants found in our non-jewish cohort were in BRCA2. Our results confirm the high level of admixture present in argentinian population, and highlight the detection of novel variants that could be typical of our region. The knowledge of them is relevant to improve patient risk assessment.

Legal entity responsible for the study: Centro Nacional de Genética Médica, ANLIS, Malbrán, Ministerio de Salud de la Nación

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1416P The change in self-perceived characteristics of health and lifestyle due to colorectal cancer screening invitation and attendance

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Background: Previous research implies that colorectal cancer (CRC) screening may have an effect on lifestyle. The aim of the current study was to evaluate the effect of CRC screening on self-perceived health and lifestyle among men and women within a randomized health-services study in Finland.

Methods: A random sample of 31951 Finnish men and women born in 1951 were randomized 1:1 for CRC screening for the first time in 2011. A random third received a questionnaire on lifestyle before and after screening in 2010 and 2012 (n = 10271). The current study population responded to the questionnaire on both years (n = 4895). Self-rated health (SRH), perceived healthiness of diet and perceived physical fitness were assessed with logistic and ordered logistic models using calendar time (2010, 2012), screening randomization and demographic characteristics as covariates.

Results: SRH, healthiness of diet and physical fitness improved over time (OR 1.32, CI 1.17–1.48, OR 1.23, CI 1.08–1.41 and OR 1.44, CI 1.28–1.60, respectively). CRC screening invitation had no effect on these measures compared to controls (OR 0.91, CI 0.74–1.12, OR 0.95, CI 0.75–1.20 and OR 1.09, CI 0.87–1.37, respectively). Women reported better health than men. However, further analysis showed that the attender women reported weaker and the attender men better health than the corresponding control groups.

Conclusions: CRC screening did not have an effect on self-perceived health and lifestyle. However, the difference between men and women both in controls and in CRC screening attendees needs further research. The randomized setting enables us to generalize of the results to the whole screening target population.

Legal entity responsible for the study: Nea Malila

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1417P Multi-gene panels: new clinical experience in hereditary breast and ovarian cancer

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Background: Mutations in BRCA1 and BRCA2 genes explain about 22% of families meeting testing criteria for hereditary breast/ovary cancer (HBOC). Next-generation sequencing based multi-gene panels allow the analysis of a high number of genes simultaneously with a high sensitivity and are currently integrated into clinical practice.

Methods: A total of 177 women/families with clinical criteria for HBOC underwent genetic testing with a 26-gene commercial panel related to hereditary cancer. The analysis included 150 women with a personal diagnosis of BC/OC meeting national consensus for testing except 7 patients that did not comply these criteria, 6 healthy women at high-risk with ≥1 BC/OC affected first-degree relative and 21 patients with a previous BRCA1/2 negative result by other techniques.

Results: A total of 11 BRCA1/2 mutations were identified three of which were previously undetected by other techniques. Mutations in other high or moderate BC/OC risk genes were found: one new mutation in RAD51D gene, two mutations in CHEK2 gene, one mutation in ATM gene, one mutation in PALB2 gene and two probably pathogenic variants in PALB2 and CHEK2 genes (according to predictors in silico). In addition, 8 variants of uncertain significance were detected. Subsequently, members of any of these 18 HBOC families started presymptomatic genetic diagnosis and prevention strategies.

Conclusions: In contrast to traditional sequential testing, the incorporation of multigene panels in our clinical practice has allowed us to obtain a more efficient genetic diagnosis on a greater number of families. Detecting actionable mutations in either previous BRCA1/2 negative or other HBOC associated families will optimize candidate identification for changes in medical management. The determination of the pathogenicity of frequent variants of uncertain significance in high or moderate penetrance genes remains the main challenge for cancer geneticists.

Legal entity responsible for the study: Hospital Santa Creu i Sant Pau

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1418P Clinical features and outcomes of reversible posterior encephalopathy syndrome following bevacizumab treatment

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Background: Reversible posterior leukoenchephalopathy syndrome (RPLS), also known as Posterior reversible encephalopathy syndrome (PRES) is a distinct clinicoradiological entity characterized by a constellation of clinical features, and a potentially devastating complication of bevacizumab treatment.

Methods: Patients were identified from the published literature using 'PubMed' databases using the terms 'bevacizumab' or 'RPLS' and 'RPES' from January 2006 to December 2016, who developed RPLS (RPES) features within 3 weeks of bevacizumab treatment, who had brain imaging findings of focal vasogenic edema and radiologic proof of reversibility.

Results: To date, a total of 22 cases of RPLS (PRES) following the administration of bevacizumab have been reported in the literature. The mean age at presentation of these patients was 50 years (range 34–74 years), 6 of whom were male and 14 female. Headaches ($n = 11$), seizures ($n = 10$), visual disturbances ($n = 9$) and nausea and vomiting ($n = 8$) were the common presenting symptoms. In a majority of patients, an increase in blood pressure from their baseline values was observed during their hospitalization. RPLS occurred in 3 patients who received bevacizumab as monotherapy and the rest had received bevacizumab in combination with other chemotherapeutic agents (oxaliplatin, $n = 8$; fluorouracil, $n = 6$; leucovorin, $n = 5$; gemcitabine, $n = 3$; paclitaxel, $n = 3$; capecitabine, $n = 3$; doxorubicin, $n = 2$; carboplatin, $n = 2$; and irinotecan, $n = 1$). In 20 out of 22 patients, PRES resolved following withdrawal of bevacizumab and strict control of blood pressure. 3 patients also received prednisolone and mannitol as part of their treatment for RPLS. However, 2 out of 22 patients could not recover from severe coma, and died.

Conclusions: A high level of suspicion for RPLS is advisable in patients who develop headache, seizures, visual disturbances, during bevacizumab treatment, either as monotherapy or in combination with other chemotherapeutic agents. These data support the need for close vigilance of neurological features and blood pressure monitoring of patients undergoing bevacizumab treatment. Prompt withdrawal of bevacizumab and blood pressure control appear to portend favorable outcomes in these patients.

Legal entity responsible for the study: OMC-BC

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1419P Deliberative democracy and cancer screening. The use of citizens' s juries in health policy decision-making

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Background: Participants in breast cancer screening programmes may benefit from early detection but may also be exposed to the risks of overdiagnosis and false positives. It is argued that citizens's juries offer important insights into how democratic deliberation could be institutionalised in contemporary political decision making processes. The aim of this deliberative democracy study was to know if Andalucia's Public Health System should offer screening mammography for women aged 50 and 69 years. We selected a citizens's jury to evaluate the reasons for their decision and to know the recommendations for politicians.

Methods: Thirteen women aged 50 and 69 years, who regularly participate in the breast cancer screening programme, agreed to participate as a jury to deliberate of the harms and benefits of this controversial topic. The participants were assembled on three consecutive days. On the first day a neutral expert trained the jury to understand the exposures during the second day of two expert witnesses positioned in favor of and against screening mammography, respectively. The third the jury deliberated, extracted its conclusions, cast its vote and exposed its recommendations for politicians. Transcription

of the text and the qualitative analysis of the information was done with the support of the ATLAS.ti software.

Results: We observed an improvement in the knowledge using analysis quantitative design. The Citizen's Jury voted 11-2. Eleven women voted yes and two did not. Women thanks for it, but there are still ignorance and confusion about breast cancer screening. There are three reasons for voting yes, for their health, for the nature of the test and for their individual freedom. There are women who argue the lack of effectiveness and the cost to justify their negative vote to mammography, at least with a universal character. Women make proposals to policymakers related to improving information, psychological care and research.

Conclusions: Spanish women have a very positive attitude to breast cancer screening although the information transmitted changes the opinion of some women, who want an informed decision making. They bet to maintain or increase the medicalization of their lives.

Legal entity responsible for the study: Dr. José Manuel Baena Cañada

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Disclosure: All authors have declared no conflicts of interest.

1420P Genetic landscape in HBOC families from Brazil: A mutational analysis

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Background: Even if 10% of breast cancers are diagnosed in the context of hereditary predisposition, for a great proportion of families the molecular mechanism of cancer predisposition remains unclear. Founder mutations with increased risk for breast and other cancers have been described in some latin American countries, but the hereditary breast and ovarian cancer (HBOC) mutational landscape remains understudied in this population of highly mixed genetic contributions. Our study aims to evaluate the contribution of germline BRCA1/2 and moderated penetrance genes mutations in the incidence of HBOC brazilian families.

Methods: This is a retrospective analysis of a series of 666 consecutive patients with HBOC syndrome who underwent genetic test between March 2007 and March 2017 in Sirio-Libanes Hospital. Clinical, pathological and sequencing available data on mutations and unclassified variants in high, moderate and low penetrance genes was analysed.

Results: The majority of the patients were tested in the context of multigene NGS pannels (69%), 205 of the patients had only access to *BRCA1/2* full gene screening. A pathogenic mutation was identified in 227 index cases (34%). Unclassified variants (UV) were present in 139 tests (19%). *BRCA1/2* mutations could explain the molecular mechanism of cancer predisposition of 133 cases (20%) while TP53 gene was the second most commonly mutated gene in our cohort (46 patients, 7%). 83% of *TP53* mutation corresponded to the brazilian *TP53* founder mutation R337H (c.1010G>A). Intermediate penetrance genes mutations were present in 22 cases (3,3%): 11 for *PALB2*, 6 for *ATM*, 4 for *CHEK1*, 1 for *BRIP1*. Mismatch repair genes were mutated in 3% of the patients. The index cases were in majority women (98%) diagnosed with breast cancer under 50 years (34%), 68 (10%) of them with bilateral breast tumors.

Table: 1420P

Gene	Pathogenic mutations (n)	UV
BRCA1	90	17
BRCA2	43	39
TP53	46	6
PTEN	0	1
CDH1	0	6
STK11	0	0
PALB2	11	5
ATM	6	13
BRIP1	2	5
CHEK2	4	10
RAD51C	1	3
BARD1	2	3
BAP1	0	3
MLH1	8	7
MSH2	7	6
PMS2	5	6
MSH6	0	11
EPCAM	0	0
BMPR1	0	0

Conclusions: For the majority of the patients the mechanism of predisposition remains unknown. All together BRCA1, BRCA2 and TP53 mutations could explain the predisposition of 27% of the index cases in our cohort.

Legal entity responsible for the study: Registro de Câncer Hereditário Brasileiro

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1421P Recommended cancer screening and vulnerable populations: results from the EDIFICE 5 survey

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Background: Based on data from the 2011, 2014 and 2016 EDIFICE surveys, we sought to identify potential links between impoverished living conditions and participation in screening in the context of organized programs (colorectal [CRC], breast [BC] and cervical cancers [CC]).

Methods: The EDIFICE observational phone surveys were conducted among representative population samples (age 40-75 yrs in 2011 [N = 1603] and 2014 [N = 1602]; age 50-75 years in 2016 [N = 1501]) using the quota method. Attitudes regarding screening were assessed in subgroups of individuals within the target age-groups for each screening program. Participation in screening and follow-up rates were assessed by asking if respondents had undergone at least one screening examination in their lifetime and within the recommended time frame (2 yrs for CRC and BC, 3 yrs for CC). Data were analyzed according to the validated EPICES vulnerability score.

Results: For CRC, over the period 2011/2014/2016, participation increased in non-vulnerable subgroups (60% vs. 63%, NS and 63% vs. 68%, $P = 0.05$) as did follow-up rates (34% vs 33%, NS and 33% vs 40%, $P = 0.01$). Participation (60%/54%/53%) and follow-up (31%/30%/31%) were stable among vulnerable individuals. Participation was lower in vulnerable vs. non-vulnerable individuals in 2014 ($P = 0.02$) and 2016 ($P < 0.01$). For BC, participation rates were stable over 2011/2014/2016, in non-vulnerable (97%/98%/98%) and vulnerable individuals (94%/96%/93%), but follow-up rates decreased (87%/85%/79% and 81%/76%/65%, respectively). In 2016, participation and follow-up rates were lower in vulnerable vs. non-vulnerable groups ($P = 0.01$, $P < 0.01$). For CC, participation rates decreased significantly from 2014 to 2016, in non-vulnerable (100%/97%, $P = 0.02$) and vulnerable individuals (98%/89%, $P = 0.02$), and follow-up stabilized (81%/79% and 64%/63%). Participation and follow-up were lower in vulnerable vs. non-vulnerable groups in 2016 ($P < 0.01$, $P = 0.01$).

Conclusions: The 2016 EDIFICE survey confirms the increasing impact of social vulnerability on recommended screening programs, particularly for CRC.

Legal entity responsible for the study: Kantar Health

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PSYCHO-ONCOLOGY

1422O CTCA toxicity scoring and EORTC quality of life questionnaire: A comparison of physicians' and patients' scoring of toxicity in the "Panther trial"

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Background: A debate on health-related quality of life (HRQoL) by patients' assessment and the assessment of toxicity by physicians in clinical trials is ongoing. The relations between these two assessments is therefore of importance. The aim of this study was to investigate the relations between toxicity items (Common Terminology Criteria for Adverse Events, version 3.0.) and items in the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30).

Methods: Data was collected in a randomised phase 3 trial, comparing dose dense vs standard administration of adjuvant chemotherapy in high-risk breast cancer patients with mostly node positive disease (Foukakis et al., 2016). Data from the assessment at the end of treatment was used. Items from the EORTC QLQ-C30, considered to be associated with CTCAE, were chosen individually by three researchers. Relations based on ordinal data were analysed by Goodman and Kruskal gamma.

Results: A total of 1428 event-free patients were included. Relations between 13 toxicities and 36 EORTC QLQ-C30 items (some with more than one toxicity) were investigated.

Table: 1422O Strong or moderate relation between toxicity and HRQoL item

Toxicity	HRQoL item	Relation
Diahorrea	q17. Have you had diarrhoea	0.53^{S} (0.47 to 0.59)
Vomiting	q15. Have you vomited?	0.50^{S} (0.39 to 0.62)
Fatigue	q10. Did you need to rest?	0.35^{M} (0.28 to 0.41)
	q12. Have you felt weak?	0.35^{M} (0.28 to 0.41)
	q18. Were you tired?	0.41^{M} (0.36 to 0.47)

^{S} = Strong relation (0.50-1.00) ^{M}= Moderate relation (0.30-0.49) There were no or weak relations between all the other toxicities and HRQoL items.

Conclusions: Few relations were found between CTCAE and HRQoL items, indicating that CTCAE does not mirror the total patient experience. Some toxicities, however, are not related to patients scoring of HRQoL and therefore have to be reported by physicians. These findings should raise concerns on how to best evaluate HRQoL/toxicities in clinical trials.

Clinical trial identification: NCT00798070 and ISRCTN39017665

Legal entity responsible for the study: Department of Oncology-Pathology, Karolinska Institutet

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1423P Loneliness and cognitive dysfunction in elderly cancer patients

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Background: The number of geriatric cancer patients is progressively increasing. The evaluation of cognitive functions is important. Loneliness is an emotional experience that results from unmet personal or social requirements. The association between loneliness and cognitive dysfunction has been well documented in elderly patients. However, there is no data in elderly cancer patients. The purpose of this study is to evaluate the association between loneliness and cognitive dysfunction in geriatric cancer patients.

Methods: Patients, more than 65 years of age, in departments of medical oncology and geriatrics were included. Patients were evaluated with structured questionnaires to define sociodemographic and clinical characteristics. In addition, patients were tested with multidimensional Scale of Perceived Social Support (PSC), UCLA loneliness Scale (ULS), standardized mini mental state examination (SMMSE), Clock drawing test and geriatric depression scale (GDS).

Results: 314 elderly patients (214 with a diagnosis of cancer and 120 without cancer) were evaluated. Scores of PSC, ULS, SMMSE were higher in patients without cancer. Median score of GDS in cancer patients was higher than non-cancer patients (4 vs 2, $p < 0.001$). The analysis of ULS and SMMSE showed a negative correlation between

Table: 1423P

Risk Factor	High Loneliness Score		Cognitive Impairment	
	RR(95%CI)	p	RR(95%CI)	p
Presence of depression	1.98(1.0- 3.6)	0.02	2.64(1.3-5.1)	0.004
Low social support	2.01(1.1-3.4)	0.01	1.1(0.5-2.1)	0.75
Educational status- low	3.0(1.3-6.6)	0.007	1.93(0.8-4.4)	0.12
>75 years old	1.46(0.8-2.6)	0.21	1.36(0.6-2.7)	0.36
Female	1.24(0.5-2.6)	0.56	0.88(0.3-2.3)	0.81
High income	1.36(0.7-2.4)	0.27	1.1(0.6-2.2)	0.63
Retired	0.64(0.2-1.4)	0.30	0.54(0.2-1.4)	0.22
Cancer diagnosis	0.93(0.5-1.6)	0.81	1.79(0.8-3.6)	0.11
Live in Rural	1.61(0.7-3.3)	0.20	1.5(0.6-3.3)	0.29
Comorbidity			1.38(0.68-2.8)	0.36
High Loneliness score			1.18(0.6-2.2)	0.61

loneliness and cognitive functions (r= -0.185, p = <0.001). The negative correlation was observed both in cancer patients (r= -0.206, p = 0.001) and non-cancer patients (r= -0.262, p = 0.002). In multivariate analysis; presence of depression, low PSC scores and low educational status were associated with high ULS scores. In the multivariate analysis of factors associated with cognitive dysfunction concluded that depression was associated with increased risk of cognitive dysfunction. (RR: 2.64 (1.3-5.1), 95% CI), p = 0.004) (Table).

Conclusions: In elderly cancer patients, cognitive functions are negatively effected by increased loneliness. However, the association between cancer diagnosis, loneliness and cognitive dysfunction couldn't be demonstrated in multivariate analysis.

Legal entity responsible for the study: Ali Alkan

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1424P The study of emotional distress in oncology patients

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Background: A study of the levels of emotional distress in patients during diagnostics and hospitalization was conducted at Petrov Oncology Scientific Research Institute in 2016. The work presented analyzes the results of the study of emotional distress in oncology patients. Groups of oncology patients, who most acutely require professional psychological aid, have been allocated.

Methods: The study is based on the modified distress self-evaluation method of International Psycho-Oncology Society (IPOS).

Results: 4,113 patients have been studied in total, of them 2,113 at the stage of diagnosis and 2,000 during hospitalization. The percentage of outpatients who report an abnormal anxiety level on the self-evaluation scale is distributed among nosology as follows: breast – 22%, gynecology – 18%, urology – 16%, unspecified diagnosis – 13%, digestive tract – 11%, lungs – 7%, soft tissue and skin tumors – 5%, and bones – 3%. The analysis of the data distribution between in-patient departments has shown that, among the patients reporting abnormal anxiety levels, 21% are hospitalized in the breast tumors department, 16% in the gynecology department, 10% in the head and neck tumors department, 9% in the radiology department, while the chemotherapy, thoracal surgery and urology departments admit 8% each, 6% are in the oncohematological department, and 5% are in the general oncology department during hospitalization.

Conclusions: More than 40% of oncology patients experience abnormal anxiety levels related to the disease, the treatment and related changes in lifestyle. The majority of patients who describe their anxiety as abnormal have breast cancer.

Legal entity responsible for the study: Kristina Kondrateva

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1425P Risk of mood disorders in long-term cancer survivors: A population-based cohort study

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Background: Evidence regarding whether long term survivors ($\geq$ 5 years) of adult cancers (LSAC) have a higher risk of mood disorders than the general population is not consistent. We aimed to compare the mood disorder rates between the two cohorts and to identify potential risk factors.

Methods: We conducted a retrospective population-based cohort study using the Taiwan National Health Insurance Research Database. We identified LSAC who were newly diagnosed between January 1, 2000 and December 31, 2007. One control was matched per patient for age, sex, index date, and the Charlson comorbidity index (CCI). The primary outcome was diagnosis of mood disorders during the follow-up period. Cumulative incidences and sub-hazard ratios (SHR) were calculated and multivariate analyses were conducted after adjusting for mortality.

Results: We identified 190,748 LSAC and 190,748 controls. The mood disorder risk was significantly higher in the LSAC cohort than in the control cohort (adjusted SHR = 1.16, 95% confidence interval [CI] = 1.13–1.18, P < 0.0001). Patients with certain cancer types were at increased risk, particularly in the first 2 years after diagnosis. However, patients with head and neck cancers or esophageal cancers had a higher risk after the 5-year follow-up period (incidence rate ratio = 1.40, 95% CI = 1.18–1.67; 2.46, 95% CI = 1.29–4.69, respectively). Multivariate analysis indicated that being female, aged 40–59 years, with more than two primary cancers, receiving two or more treatment modalities, having CCI scores higher than 3, a higher urbanization level, and lower monthly income were independently associated with an increased risk of mood disorders.

Conclusions: Long-term cancer survivors have an increased risk of mood disorders and therefore should be followed-up for depresison especially in those with certain site-specific cancer types.

Legal entity responsible for the study: Wen-Kuan Huang

Funding: Chang Gung Medical Foundation, Chang Gung Memorial Hospital at Linkou

Disclosure: All authors have declared no conflicts of interest.

1426P What oncologists should know about the screening of psychological distress: One example of pilot study in Ancona

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Background: Screening for psychological distress is one of the most important steps in Psycho-Oncology research and clinical assistance. In our Institution, before the present study, four studies have been carried out in this area from 2013 to 2016: 441 people were screened and 881 questionnaires were administered.

Methods: The study has been carried out using the following tools: Needs Evaluation Questionnaire (investigates five areas: informative needs, needs related to assistance and care, relational needs, needs for psycho-emotional support, material needs); Beck Depression Inventory II (BDI II), both for caregivers and for patients; Mini Mental Adjustment to Cancer (MiniMac, for the copying style); State-Trait Anger Expression Inventory–2 (for the expression of anger).

Results: From February to April 2017, 78 people have been screened (44 patients and 34 caregivers; Male/female ratio was 29/49; median age was 54 years (range 21-84); 32% of patients showed informative needs, 48% indicated a psychological need, 18% assistance needs. Depression was more present in patients (30%) than in the caregivers (22%) and problems concerning sleep (65%) and fatigue (60%) were more common; only 61% of patients had a fighting spirit while 24% of caregivers showed a high expression of anger. Fischer test showed a correlation between anxious preoccupation (MiniMac) and symptomatic depression (P = 0,000432860); moreover, Helpless-Hopeless copying style was also related (P = 0,005396636) to depression; caregiver's expression of aggressiveness (P = 0,114394682) to patients' anxious preoccupation. The relationship between patients' depression to caregivers' aggressiveness requires further investigation (P = 0,247399740).

Conclusions: Psychological screening can fulfill the following aims: discover expressed needs, coping styles, depression, familiar distress, burden. The results and the correlations underline the importance of managing the patients' anxiety and the expression of the caregivers' aggressiveness and the relationship of such issues with depression. Moreover, informative needs are associated to the most diffused psychological needs.

Legal entity responsible for the study: Clinica Oncologica Ancona

Funding: Fondazione Rossetti-Fedecostante Ancona

Disclosure: All authors have declared no conflicts of interest.

1427P Biopsychosocial factors underlying older patients treated for an incurable cancer in a two-tiered health care system in Brazil

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Background: Patients with advanced cancer experience symptoms that include pain, fatigue, and depression. We sought to describe prevalence and identify factors associated with biopsychosocial distress in older patients (65+) diagnosed with cancer stage IV.

Methods: Participants were recruited from two different types of health care facilities, public [PUB] and private [PRI] institutions, in Brazil. A cross-sectional analysis of common biopsychosocial symptoms (anxiety, depression, pain, and fatigue), and quality of life reported by older patients undergoing chemotherapy treatment was performed.

Results: Older patients (n = 167) were enrolled (Mean age=73; SD = 5.6); 59.3% from PUB. Majority were female (56.3%; 38.9% PUB), white (68.9%; 35.7% PRI, p<.01), married (59.3%; 32.1% PUB, p<.01); and diagnosed with GI (29.9%; 15.8% PUB), GU (16.2%; 4.9% PUB), and hematologic (13.8%; 7.5% PRI) cancers. Almost 16% of patients reported depression symptoms (9.6% PUB) and 12% of anxiety (8.4% PUB). PUB patients also reported associated lower QOL, which is at 50th percentile of the US

norm (PRI is at 75th percentile). PUB patients reported significantly more biopsychosocial problems including distress (21.6% vs 7.2%), pain (28.1% vs 12.0%), fatigue (34.7% vs 16.8%), sleep (22.8% vs 15%), neuropathy (22.8% vs 8.4%), and financial toxicity (16.2% vs 5.4%), compared to patients treated at PRI (all $p < 0.05$). Mostly pain (B = 1.8; B=-6.6), fatigue (B = 0.8; B=-6.5) and sleep (B = 1.2; B=-8.3) were associated with moderate to severe distress and worst QOL (all p<.01).

Conclusions: Older patients with late-stage cancer in Brazil suffer substantial unrecognized morbidity which impacts their distress and QOL. Biopsychosocial screening for older patients should be included in quality cancer care. Moreover, patients treated within PUB show worse outcomes than PRI counterparts, and they are at higher risk for multiple physical, psychological, and financial morbidity. Earlier initiation of biopsychosocial screening with appropriate supportive care may improve their QOL.

Legal entity responsible for the study: Cristiane Decat Bergerot

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1428P Family-associated factors influence the postoperative prognosis in patients with non-small cell lung cancer

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Background: The relationship between family-associated factors and the postoperative prognosis is unknown in patients with non-small cell lung cancer (NSCLC). We hypothesized that family-associated support was associated with postoperative prognosis via nutritional pathway. The aim of this study is to elucidate the relationship between family-associated factors and postoperative prognosis in patients with NSCLC.

Methods: We selected 195 patients with NSCLC who underwent curative surgery between 2005 and 2010 whose computed tomography images within 1 month preoperatively and after 1 year postoperatively were available. The nutritional indices such as prognostic nutritional index (PNI), controlling nutritional status (CONUT), modified Glasgow prognostic score (mGPS) and skeletal muscle area (SMA) were used to estimate the change in nutritional condition after 1 year postoperatively. Paravertebral muscle area at the 12th thoracic vertebra level was used to analyze the SMA.

Results: One hundred and forty-four patients (73.8%) had both children and a partner. Twenty-seven (13.8%) only had children and 14 (7.2%) only had a partner. Childless patients showed a significantly shorter overall survival (OS) and disease-free survival (DFS) than those with children ($p<0.05$ and $p<0.05$, respectively). The postoperative exacerbation of PNI, CONUT, mGPS and SMA were found to be significantly correlated with childless patients compared with those with children ($p=0.002$, $p=0.001$, $p<0.001$ and $p=0.029$, respectively). Childless patients with a partner showed a particularly shorter OS and DFS than those with children ($p<0.001$ and $p<0.001$, respectively). The childless patients with a partner showed significant postoperative exacerbation of PNI, CONUT, mGPS and SMA compared with those with children ($p=0.037$, $p<0.001$, $p<0.001$ and $p=0.039$, respectively).

Conclusions: The patients without any children had a significantly poorer postoperative prognosis than those with children. The childless partner-present patients showed a particularly shorter OS and DFS than those with children. It was suggested that the childless patients were significantly associated with postoperative exacerbation of the nutritional status.

Legal entity responsible for the study: Shinkichi Takamori

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1430P Sexual functioning and quality of life in Egyptian premenopausal patients receiving treatment for breast cancer

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Background: In Egypt, due to cultural reasons, breast cancer patients may suffer in silence struggling with their sexual problems. This is the first study to explore the sexual functioning of Egyptian breast cancer patients receiving anti-cancer treatment.

Methods: The study included 105 married premenopausal patients aged ≤55 years, who underwent surgery and were receiving adjuvant treatment. We used the Arabic validated versions of the EORTC quality of life questionnaire (EORTC QLQ-C30, v 3.0) and the breast cancer module (EORTC QLQ-BR23) to assess quality of life and the female sexual function index (FSFI) to assess sexual functioning.

Results: The median age of patients was 43 years, 11% of them were employed, 81% were literate and 98% were circumcised. The average FSFI score was 16 (±9). The FSFI differed significantly according to systemic treatment ($p = 0.007$). Patients receiving chemotherapy had the lowest score (12 ± 8.5) and those receiving tamoxifen had the highest (18 ± 8.5). The FSFI score did not differ according to the type of surgery ($p = 0.892$). However, the body image scale of EORTC QLQ-BR23 was significantly better among patients who underwent breast conservative surgery compared to modified radical mastectomy ($p = 0.004$). There was a significant positive correlation between the FSFI score and the scores of global health status ($p < 0.001$), physical functioning ($p = 0.002$), role functioning ($p < 0.001$), emotional functioning ($p = 0.004$), social functioning ($p = 0.041$) scales of EORTC QLQ-C30 and body image ($p < 0.001$) and future prospective ($p < 0.001$) scales of EORTC QLQ-BR23. There was a significant negative correlation between the FSFI score and scores of fatigue ($p = 0.001$), pain ($p = 0.006$) and appetite loss ($p = 0.028$) scales/items of EORTC QLQ-C30 and systemic therapy side effects ($p = 0.003$) scale of EORTC QLQ-BR23.

Conclusions: The current results suggest that Egyptian breast cancer patients receiving chemotherapy experience significant sexual dysfunction. The type of surgery has no direct effect on sexual functioning, but may affect it indirectly through its impact on body image satisfaction. Overall, sexual dysfunction is strongly related to the quality of life in this group of patients.

Legal entity responsible for the study: Ain Shams University, Cairo, Egypt

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1431P Primary results of a study to evaluate a decision aid for women offered neoadjuvant systemic therapy for breast cancer

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Background: Women diagnosed with large or highly proliferative operable breast cancer may be offered neoadjuvant systemic therapy (NAST) for reasons including downstaging, prognostication or expanding surgical options. We aimed to systematically develop, and evaluate a DA for women who had been offered NAST.

Methods: Eligible women who were considered candidates for NAST, from four Australian recruiting centres were enrolled in a single arm longitudinal study. Participants completed online questionnaires prior to accessing the DA, and on three occasions post-DA. Primary outcomes were feasibility of use, and acceptability to patients and clinicians. Secondary outcomes were patient reported measures relevant to patient decision-making.

Results: Seventy-nine women were offered study participation and 59 enrolled. Patients were typically well educated, married, had health insurance and were information seekers (mean information needs: 7.5/10; SD 1.84). 59/79 (74.7%) patients who were offered study participation accessed the DA and 49 (79.7%) of those 59 participants reported having read it. 41/51 (80.4%) participants who completed the post-DA assessment reported that the DA helped them with their decision about NAST. 51/59 (86%) participants elected to receive NAST. 16/18 (88.9%) investigators would continue to use the DA in routine practice. Post-DA, decisional conflict decreased significantly across all subscales ($p < 0.01$); anxiety and distress decreased significantly; 86.3% achieved at least as much decisional control as they desired; a high level of knowledge was demonstrated; and 39/51 (76.5%) patients had a high (≥24) Satisfaction with Decision score (mean 25.5, SD 3.6). 84.4% reported that they shared responsibility for the decision about NAST. Investigators reported that the DA was able to be integrated into patient care.

Conclusions: Study primary outcomes were positive, showing the DA was feasible and acceptable to patients and clinicians. Improvements in decision-related outcomes were demonstrated, and the DA could be included in routine workflow. This DA can be implemented into routine clinical practice for women with operable breast cancer who are candidates for NAST.

Clinical trial identification: Registration: Australia and New Zealand Clinical Trials Registry (www.anzctr.org.au): ACTRN12614001267640

Legal entity responsible for the study: Australia and New Zealand Breast Cancer Trials Group

Funding: HCF Research Foundation Australia and New Zealand Breast Cancer Trials Group

Disclosure: All authors have declared no conflicts of interest.

1433P Burnout syndrome: What impact on clinical research?

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Background: Burnout is a job-related psychological syndrome causing depersonalization, emotional exhaustion and lack of personal accomplishment. Albeit studies mainly focus on professionals who have a direct contact with patients, physicians and nurses, little is known about burnout among other professionals employed in clinical research, that requires stressful efforts to maintain quality standards. We decided to evaluate perceived and actual burnout levels experienced by professionals who are at the "bottleneck" of research: Clinical Research Coordinators (CRCs).

Methods: The Gruppo Italiano Data Manager spread an anonymous questionnaire among about 130 CRCs. The survey consisted of 8 items on workload and perceived stress levels and a specific burnout test developed by a group of Italian psychologists.

Results: The survey was completed by 36% of subjects. On average, interviewed CRCs work 42 hours/week and follow 25 studies; 89% feel stressed and 64% believe that this affects negatively the quality of their work. Moreover, 57% of CRCs declare that this condition may soon cause a job change. The major sources of stress are: contract type (43%); workload (17%); lack of skills recognition (11%). Interestingly, the factor that most frequently has been identified among the first 3 causes of stress is the contract type (81%), followed by lack of skills recognition (32%). Based on the psychological test, the average stress level of the sample is 68 points out of overall 225; the highest levels pertain the emotional (average: 17.0/45) and physical spheres (16.3/45), while the social area is the least affected (9.7/45). Stress levels show only a very weak correlation with workload (Pearson coefficient = 0.062) and hours worked (0.095).

Conclusions: Albeit almost all CRCs perceive high levels of stress, psychological testing shows a medium-low degree of burnout. An explanation could be that CRCs are settled into distressing work conditions, so this no longer results in burnout. Burnout was substantially uncorrelated to quantitative estimates of workload, rather depending on other, qualitative, factors, such as lack of skills recognition and contractual instability. Lastly, our data suggest that current workload evaluation methods, mainly based on the number of followed studies, are no longer appropriate.

Legal entity responsible for the study: Gruppo Italiano Data Manager (GIDM)

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1434TiP Effectiveness of the HuCare Quality Improvement Strategy on health-related quality of life in patients with cancer: Study protocol of a stepped wedge cluster randomized controlled trial (HuCare2 study)

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Background: Our group previously demonstrated the feasibility of the Hucare Quality Improvement Strategy – HQIS, aimed at integrating into practice 6 psychosocial interventions recommended by international guidelines. This trial will assess whether the introduction of the strategy in oncology wards improves patient Health-related quality of life (HRQoL).

Trial design: Multicenter, incomplete stepped-wedge cluster randomized controlled trial, conducted in three clusters of 5 centers each, in three equally spaced time epochs. The study also includes an initial epoch when none of the centers is exposed to the intervention, and a final epoch when all centers will have implemented the strategy. The intervention is applied at a cluster level, and assessed at an individual level with cross-sectional model. 720 patients who received a cancer diagnosis in the previous 2 months and about to start medical treatment will be enrolled. Primary aim is to evaluate the effectiveness of the HQIS vs standard care in terms of improvement of at least one of two domains (emotional and social functions) of HRQoL using the EORTC QLQ-C30 questionnaire, at baseline and at 3 months. This outcome was chosen because cancer patients generally exhibit low HRQoL, particularly at certain stages of care, and because it allows to assess the strategy's impact as perceived by patients themselves. The HQIS comprises three phases: 1) clinician training - to improve communication-relational skills and instruct on the project; 2) center support – 4 on site visits by experts of the project team, aimed to boost motivation, help with context analysis and identification of solutions; 3) implementation of EBM recommendations at the center.

Clinical trial identification: NCT03008993

Legal entity responsible for the study: Italian Association of Medical Oncology (AIOM)

Funding: Association of Medical Oncology (AIOM); MEDeA (non-profit volunteer association)

Disclosure: All authors have declared no conflicts of interest.

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

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PUBLIC HEALTH

1440PD The European Cancer Patient Coalition's white policy paper on the value of innovation in oncology

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Background: Each year, over 3 million Europeans are diagnosed with cancer, and over 1 million Europeans die from the disease. With a growing and ageing population, action is urgently needed to address this major global health and societal concern. Action is needed to help policy-makers understand how they can improve access to innovative cancer care and treatment. Aim: To produce a policy white paper that summarised the major recommendations to improve access to innovative cancer care and treatment for Europeans diagnosed with cancer.

Methods: The European Cancer Patient Coalition developed the white paper over a one-year period, in collaboration with Interel Public Affairs, oncology experts, and the patient organisations that form the membership of the European Cancer Patient Coalition.

Results: The "Value of Innovation in Oncology" white paper presented the position of the European Cancer Patient Coalition on innovation in oncology, and offered recommendations to help reduce variations in access to innovation and to involve patients in decision-making. It summarised the European Cancer Patient Coalition's stance on topics related to innovation in oncology, with the overarching goal to shrink international variations in the time to patients' access to innovation in oncology, while, at the same time, it considered the sustainability of health systems and how to ensure innovation is celebrated and accessed appropriately. Finally, the paper focused on recommendations to increase the involvement of patients in key aspects of innovation, including assessment and access.

Conclusions: More work is needed at the European and national level to improve the access of Europeans with cancer to innovative treatment and care and to ensure that people with cancer are actively involved in decisions throughout the care pathway.

Legal entity responsible for the study: European Cancer Patient Coalition

Funding: Bristol-Myers Squibb, Eli Lilly and Company, MSD, Novartis, Pfizer, and Roche.

Disclosure: L. Makaroff, A. Rek, I. Manneh-Vangramberen, F. Florindi: Employee of the European Cancer Patient Coalition F. De Lorenzo: President of the European Cancer Patient Coalition K. Apostolidis: Vice President of the European Cancer Patient Coalition J. Pelouchova: Secretary of the European Cancer Patient Coalition A. Winterbottom: Treasurer of the European Cancer Patient Coalition S. Chrostowski, D. Cimpoeru, N. Bolanos Fernandez: Board member of the European Cancer Patient Coalition L. Baker: Employee of Interel Public Affairs Belgium. Clients of Interel Public Affairs include some pharmaceutical companies. The European Cancer Patient Coalition has received support from Merck, Pfizer, Roche, MSD, Bristol-Myers Squibb, AbbVie, Amgen, AstraZeneca, Baxter, BI, Celgene, Helsinn, Ipsen, Lilly, & Novartis.

1441PD Magnitude of clinical benefit of randomized controlled trials supporting US Food and Drug Administration approval of drugs for solid tumours

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Background: The European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) is a validated and reproducible tool to assess the magnitude of clinical benefit from drugs for solid tumors. Here, we evaluate characteristics and outcomes of clinical trials supporting approval by the FDA and their association with ESMO-MCBS.

Methods: We searched the Drugs@FDA website for applications of anticancer drugs from January 2006 to December 2016. Drug labels and reports of registration trials were reviewed and study characteristics, efficacy, toxicity and quality of life outcomes as well as regulatory pathways were collected. For randomized controlled trials (RCTs) ESMO-MCBS grades were applied. Meaningful clinical benefit was defined as a grade of A or B for trials of neo/adjuvant intent and 4 or 5 for those of palliative intent. Comparisons between groups were assessed using Logistic regression and the Mann Whitney U test.

Results: We identified 137 studies; 109 (80%) of which were RCTs. These led to the approval of 63 individual drugs for 118 licensed indications. Among the 105 RCTs for which the ESMO-MCBS could be applied, 7 (6%) were in the neo/adjuvant setting and 98 (94%) in the palliative setting. Only 46 (44%) met the ESMO-MCBS clinically meaningful benefit threshold (100% of neo/adjuvant trials and 41% of palliative trials). In multivariable analysis of palliative therapy trials, meaningful ESMO-MCBS grades were associated with phase III trials (compared to phase II; OR 38.45, $P = 0.004$), those with overall survival as their primary endpoint (compared to intermediate endpoints; OR 8.28, $P = 0.001$) and trials of targeted drugs with companion diagnostics (OR 11.62, $P < 0.001$). Over time, there has been an increase in the number of trials meeting the ESMO-MCBS threshold (33% in 2006 vs. 67% in 2016, P for trend = 0.04). There was an insufficient number of neo/adjuvant studies to perform statistical analysis.

Conclusions: In patients with advanced solid tumours, fewer than half of RCTs supporting FDA approval meet the threshold for clinically meaningful benefit using validated scales.

Legal entity responsible for the study: None

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Disclosure: All authors have declared no conflicts of interest.

1442PD Review on adherence to breast cancer guidelines in Europe

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Background: Morbidity and mortality from breast cancer in Europe, as well as costs associated with the disease, remain high. Patients treated according to existing guidelines have better survival. The European Commission Initiative on Breast Cancer (ECIBC) aims to improve quality of care by developing evidence-based breast cancer guidelines and supporting their implementation via a quality assurance scheme for breast cancer services. The goal of this study is to give an overview on compliance with breast cancer guidelines in Europe.

Methods: Studies assessing adherence to guidelines on breast cancer screening, diagnosis, treatment and follow-up were searched via Pubmed. Studies published between 1990 and 2016 were included.

Results: In total, 127 studies (mainly observational, retrospective, prospective, and cross sectional) were analysed. The number of participants varied from 56 to 72 000—with studies based on cancer registry data typically including more than 10 000 patients. Overall, adherence to guidelines was variable. Regarding treatment, (e.g. chemotherapy) adherence ranged from 70% to 96% and was approximately 50% for follow-up. Additional or 'unnecessary' procedures were cited as the main causes of non-compliance to follow-up. On the other hand, adherence with respect to radiotherapy (e.g. compliance with technical guidelines) and some safety-related aspects (e.g. cardiac monitoring during adjuvant trastuzumab therapy and prophylaxis with colony-stimulating factors) was substantially lower. Elderly patients were treated less frequently according to existing guidelines. Professionals with less experience (i.e. < 8 years) complied better with guidelines. Use of computerised decision support systems (CDSS) and implementation of a multidisciplinary breast cancer pathway led to better compliance.

Conclusions: In Europe, adherence to guidelines is variable. Implementation of guidelines can help decrease variability in clinical practice, and improve treatment effectiveness and patient safety. Fortunately, adherence can be monitored through the use of quality assurance schemes (e.g., the ECIBC). Incorporating a CDSS within the clinical workflow could reduce the workload of physicians and thus increase their compliance with guidelines.

Legal entity responsible for the study: European Commission, Directorate General Joint Research Centre European Commission, Directorate General Joint Research Centre.

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Disclosure: All authors have declared no conflicts of interest.

1443PD Analysis of compliance factors for colorectal cancer screening using a Bayesian network

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Background: Compared to standard explanatory analyses based on multivariate regressions, Bayesian network analyses enable multiple hypotheses and clear graphical representations of complex interactions. They provide visual descriptions of causal pathways to distinguish between direct/indirect factors. We compared multivariate regression and a Bayesian network to assess factors associated with colorectal cancer (CRC) screening.

Methods: The 5th French observational survey, EDIFICE 5, was conducted (Nov 22-Dec 7, 2016) by phone interviews of a representative sample of 1501 individuals (age, 50-75 y). The present analysis focuses on 1299 individuals with no history of cancer (50-74 y). Bayesian analysis was performed with the bnlearn R Package. Parameters of the Bayesian analysis were based on the literature and our own data (logistic regression). "Blacklist/whitelist"-type restrictions were used to reset current understanding of the correlations between variables. We also analyzed the network topology.

Results: In our sample, 36% (N = 469) declared never having undergone CRC screening (colonoscopy, fecal occult blood test) in their lifetime. The Bayesian model revealed 5 direct correlating factors: age, smoking status, social vulnerability, psychological reassurance in the screening test (PRST), and confidence in the efficacy of the test. The latter 2 account for 43% of the observed sum of the mutual informations. Other relevant factors typically seen in the literature and regression analysis had an indirect impact: level of education, self-perception of own risk of CRC, gender, temporal perspective, confidence in their physician and fear of the disease. Multiple regression analysis identified PRST (OR = 0.84, 95% CI 0.80-0.88, $P < 0.01$) and fear of the disease (OR = 0.90, 95% CI 0.84-0.96, $P < 0.01$) as the two main criteria.

Conclusions: We showed that Bayesian network analysis provides a novel representation of factors associated with CRC screening, and may explain why interventions focusing on indirect factors might be ineffective if the next step of the causal pathway remains unchanged. We suggest that Bayesian networks should be used more often to drive timely interventions (short term vs long term).

Legal entity responsible for the study: Kantar Health

Funding: Roche

Disclosure: F. Eisinger, J-Y. Blay, A. Cortot, L. Greillier, S. Couraud, J-F. Morere: Honorarium fees from Roche Edifice surveys were funded by Roche S.A. C. Lhomel: Employee of Roche. All other authors have declared no conflicts of interest.

1444PD Cancer Clinical Practice Guidelines: Evaluation of ESMO, NICE and SIGN diversity

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Background: This research study is on the critical appraisal of the impact of cited research evidence underpinning the development of cancer clinical practice guidelines (CCPGs) by the professional bodies of the European Society for Medical Oncology (ESMO), the National Institute for Health and Care Excellence (NICE) and the Scottish Intercollegiate Guidelines Network (SIGN).

Methods: A total of 101 CCPGs were identified from ESMO, NICE and SIGN websites across 13 cancer sites. Their 9,486 cited references were downloaded from the Web of Science© Clarivate Group database and analysed on Excel© (2016) using VBA macros.

Results: ESMO CCPGs mostly cited research from Western Europe while the NICE and SIGN ones from the UK, Canada, Australia and Scandinavian countries. The ESMO CCPGs cited more recent and basic research (e.g. genetics), in comparison to NICE and SIGN CCPGs where older and more clinical research (e.g. drugs treatment) papers were referenced. This chronological difference in the evidence-base is also in line with that ESMO has a shorter gap between the publication of the research and its citation on the CCPGs. It was demonstrated that ESMO CCPGs report more chemotherapy research while the NICE and SIGN more surgery, with the results being statistically significant. Also, breast cancer research was explored individually across the analysed evidence-base, with a similar pattern to overall oncology CCPGs. Additionally, the volume of breast cancer research cited by ESMO was slightly higher than the fraction of the oncology population suffering from breast cancer in Europe; for the NICE and SIGN the citation percentage was twice as much as the UK disease burden, indicating a potential preference on breast cancer among other oncology types.

Conclusions: This study showed that ESMO, NICE & SIGN differ in their evidence-base. Healthcare professionals should be aware of this heterogeneity in effective decision-making of tailored-treatments to patients irrespective of geographic location across Europe. Considering the potential of the United Kingdom exiting the European Union, a closer collaboration between these professional bodies can lead to the use of more evidence-based, relevant and updated clinical practice guidelines.

Legal entity responsible for the study: Elena Pallari, King's College London

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1445P Inclusion of older patients with colorectal cancer in clinical trials: the SAGE prospective multicenter cohort study

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Background: Whereas older patients represent the major part of new cancer cases, their underrepresentation in clinical trials leads to weak external validity. The main objective was to assess the proportions of older patients for whom there is an ongoing clinical trial available, eligible to at least one trial, invited to participate and finally included. Secondary objective was to investigate associated factors.

Methods: The SAGE multicenter prospective cohort study settled up in 7 centers in Paris Area between 2013 and 2016. All patients aged 65 years or more with a colorectal cancer were included. The endpoints were 1) the presence of at least one ongoing clinical trial available regarding stage and tumor location 2) the patient's eligibility 3) invitation and 4) inclusion.

Results: 577 patients (mean age: 75.6 years +/-7; 56% of men; 74% of colon tumor; 40.9% with metastasis) were included; 37 trials were ongoing (9 trials in median per center; academic sponsors: 62.2%; phaseI/II: 59.5%; chemotherapy: 75.7%). Overall, 12.3% of patients were included in a trial (65-69 yrs class: 19.1%; 70-75 yrs: 14.9%; 75-79 yrs: 12.8%; 80 yrs or more: 2.6%; $p < 0.001$). 18% (103/577) had none available trial for his/her stage and tumor location; among patients with available trial, 73% (347/577) were non-eligible; from the remaining, 34% (43/127) were not invited; from the remaining, 19%(17/88) refused to participate. Non-eligibility was, by order of frequency, related to tumor characteristics (31%), requested para-clinical exams (19%), history of anti-cancer treatment (15%), comorbidities (13.5%), functional status (10%) and age (5%). Among eligible patients, increased age, Performans Status and decreased Body Mass Index were independently associated with non-invitation (Table). Among patients invited to participate, patient's refusal was not associated with age.

Table: 1445P Factors independently associated with non-invitation to clinical trials in older eligible patients

Variables	Adjusted Odds Ratio (95%CI)*	P
Age, years 65-60	Reference (1.00)	0.01
70-75	0.26 (0.07-0.90)	
75-80	0.23 (0.06-0.96)	
> 80	0.05 (0.01-0.29)	
PS 0	Reference (1.00)	0.02
1	0.19 (0.06-0.62)	
≥ 2	0.50 (0.09-2.75)	
Body Mass Index, kg/m^2 21-24.9	Reference (1.00)	0.09
< 21	0.25 (0.07-0.90)	
≥25	0.76 (0.24-2.42)	

*Hierarchical multivariate logistic regression with the patient at the level 1 and the center at the level 2 and adjustment for all variables listed in the table, the number of trials in the center and the number of chemotherapy trials.

Conclusions: Inclusion of older cancer patients decreased dramatically after 80 years. Non-eligibility was the main reason for non-inclusion but rarely related to chronological age. Moreover, one-third are non-invited to participate and one-fifth refused.

Clinical trial identification: NCT01754636

Legal entity responsible for the study: AP-HP (Assistance Publique - Hôpitaux de Paris)

Funding: French Ministry of Health - PHRC

Disclosure: All authors have declared no conflicts of interest.

1446P Risk of second primary cancers and competing mortality in survivors of adult-onset cancer: changing pattern over three decades

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Background: Survivors of first adult-onset cancers are at risk of developing second primary cancers (SPCs) and are at risk of death from their subsequent cancers and other competing causes. Here we investigated patterns of incident SPC risk and cause-specific mortality in survivors of adult-onset cancer during the past three decades.

Methods: Data were extracted from the population-based Tasmanian Cancer Registry in Australia. Patients diagnosed with a first primary cancer between 1980 and 2009 were followed for incident SPCs to December 31, 2013 and for deaths to December 31, 2014. SPC risks were quantified by using standardised incidence ratios (SIRs). Trends in SPC risk over time were assessed in multivariable Poisson models. The cumulative incidence and subdistribution hazard ratios (SHR) of cause-specific deaths were estimated using competing risk models.

Results: 5,339 SPCs were observed from 51,802 cancer survivors. The SIRs for any SPC increased from 0.98 with a first cancer diagnosis in 1980-1984 to 1.12 in 2005-2009. The increase in SIRs was significant in multivariable Poisson models (Ptrend$<$ 0.001). Deaths were identified in 39,976 (69.8%) of 57,288 patients. The 5-year cumulative incidence of death due to first primary cancer gradually decreased from 57.2% for a first cancer diagnosis in 1980-1984 to 30.7% in 2005-2009. However, the 5-year cumulative incidence of deaths due to subsequent cancers varied across periods of first cancer diagnosis, with an increase from 1.0% in 1980-1984 to 1.7% in 1995-1999, and a decrease to 1.4% in 2005-2009. The SHR of deaths due to first primary gradually decreased over time in multivariable competing risk models, but varied over time for deaths due to subsequent cancers: the SHR increased from 1.00 (reference) in 1980-1984 to 1.19 (95%CI 1.03-1.36) in 1995-1999, then decreased to 0.80 (95%CI 0.69-0.94) in 2005-2009.

Conclusions: The risk of SPC has increased in Tasmania over the last three decades. While the risk of death due to first primary cancer decreased over time, the risk of death due to subsequent cancers did not. The increased risk of deaths from subsequent cancers might be an outcome of overdiagnosis of first primary cancer in the 1990s.

Legal entity responsible for the study: Menzies Institute for Medical Research, University of Tasmania

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1447P Reporting of results of randomized trials in common cancers in the lay media

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Background: Limited data exist about the role of the lay media (including the financial press) in the dissemination of results of randomized controlled trials (RCTs) in common cancers.

Methods: We searched clinicaltrials.gov to identify phase III RCTs evaluating new drugs in breast, colorectal, lung and prostate cancer. We included all completed and active trials that have completed accrual between 1 January 2005 and 31 October 2016. Reporting of trials in the lay media was identified by a systematic search of Lexis-Nexis Academic using the name of the drug and trial. Scientific reporting was defined as presentation at a conference or publication in full in the scientific literature. Associations between reporting in the lay media before scientific reporting and study design, results and sponsorship were evaluated using logistic regression.

Results: Of the 180 RCTs identified, 55% were positive, 79% were performed with palliative intent and 79% evaluated targeted therapies (including endocrine and immunotherapy). We identified 93 (52%) reports in the lay media (66% of positive trials and 38% of negative trials). In 49 cases (27%) reporting in the lay media occurred before scientific reporting with an increasing trend over time ($p = 0.009$). Among these, 53% presented quantitative data. The median time between lay media reporting and scientific reporting was 16 weeks (range 1-220 weeks). Reporting in the lay media before scientific reporting was associated with positive results (OR 3.12, $p < 0.001$), industry compared to academic sponsorship (OR 3.20, $p = 0.04$), palliative intent (OR 2.84, $p = 0.04$), journal impact factor of full publication (OR 1.02, $p = 0.03$), evaluation of targeted therapy compared to chemotherapy (OR 3.70, $p = 0.05$) and prostate cancer compared to breast cancer (OR 4.86, $p = 0.003$). There was no association between early reporting in the lay media and study endpoint, or quantitative reporting.

Conclusions: Over a quarter of all RCTs in common cancers are reported in the lay media before they are reported scientifically. Positive trials, industry sponsorship, palliative intent, journal impact factor and evaluation of new targeted therapy, especially in prostate cancer are associated with early reporting in the lay media.

Legal entity responsible for the study: Eitan Amir

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1448P Effect of rural residence (RD) and distance travel to the cancer center (DTC) on neoadjuvant chemoradiation (NCRT) in localized rectal cancer

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Background: Neoadjuvant chemoradiation therapy (NCRT) has been associated with a lower rate of local recurrence and represents an accepted standard of care. Yet, access to treatment or decisions about treatment can be affected by contextual factors such as rural residence (RD) and distance travel to cancer center (DTC). In the current study, we evaluated relationship between RD and DTC and NCRT.

Methods: A cohort of patients diagnosed with localized rectal cancer during 2009-2013 in the province of Saskatchewan was studied. The logistic regression analyses were performed to assess relationship between RD and DTC and lack of NCRT.

Results: Total 279 patients were identified with median age of 66 yrs (IQR:59-76) and M:F of 1:0.71. 94 (33.6) had a major comorbid illness. 183 (65%) were rural resident. The median DTC was 141 km (IQR 7-233). Of 279 patients, 116 (41%) were referred for NCRT, 161 (58%) underwent upfront surgery, and 2 declined surgery. The mean DTC for group treated with NCRT was 111.5 $\pm$122km compared with 169.0$\pm$176km if they did not receive NCRT ($p = 0.001$). Of urban resident, 52/96 (54%) were referred for NCRT compared with 64/183 (35%) of rural resident ($p = 0.002$). After excluding 33 (12%) patients who had clinical stage I disease and underwent upfront surgery, a univariate regression analysis revealed that both DTC (OR 1.92, 95% CI: 1.15-3.20) and RD (OR 2.51, 95%CI: 1.46-4.32) were significantly correlated with lack of NCRT. On multivariate analysis following relationships were noted with lack of NCRT. Age $\geq$ 70 yrs (OR 1.45, 95%CI: 0.84-2.45), comorbid illness (OR 1.52, 0.86-2.67), ECOG performance status of $>$ 1 (OR 1.25, 0.49-3.17), DTC (OR 1.07, 0.51-2.23), and RD (OR 2.56, 1.17-5.57).

Conclusions: Our results revealed that RD but not DTC is associated with a lower rate of NCRT in patients with localized rectal cancer. Future studies are required to explore the underlying cause of differential referral.

Legal entity responsible for the study: Saskatchewan Cancer Agency

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1450P European survey of 907 people with cancer about the importance of nutrition

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Background: Nutritional and metabolic disorders are highly prevalent among cancer patients. We aimed to analyse the dimension of nutritional alterations among cancer patients and survivors in Europe by using a structured questionnaire encompassing the perspectives of patients and their physicians on nutritional issues.

Methods: A structured questionnaire was designed to analyse the importance of nutrition for people with cancer. The questionnaire was subdivided in specific areas of interest, such as the presence of feeding problems, perception of nutrition importance, role of food supplements, and their view of their physician's approach to nutrition. All cancer patients and survivors were eligible to answer the questionnaire, except for people diagnosed with brain and breast cancer. The study was conducted by the European Cancer Patient Coalition (ECPC), Sapienza University of Rome, and Healthware International. ECPC ensured the dissemination of questionnaire to its Members in 10 countries, who translated and disseminated the questionnaire.

Results: The survey was answered by 907 cancer patients and survivors. 59.2% (n = 537) of respondents were diagnosed with cancer less than 3 years ago, and 46.2% (n = 419) were treated for cancer for 1 year or less (46.2%; n = 419). 82.4% of respondents (n = 689) believed it was important to maintain physical activity during cancer treatment, although only 53.8% (n = 450) of the respondents reported that their physicians advised them to do so. 72.9% (n = 603) of the respondents didn't know the meaning of the term "cachexia", and 92.4% (n = 764) did not receive any information about cachexia from their health professionals. 69.7% (n = 586) of respondents reported that they lost weight after the cancer diagnosis, and for 36.7% (n = 309) of respondents this loss was moderate to severe.

Conclusions: Most people with cancer surveyed reported that they would like to receive more information about how to improve their nutrition during and after treatment. There is a need to empower individual patients and patient associations by producing more information on cancer patients' nutritional needs. Such information material should be produced by patients in close collaboration with medical oncologists and other healthcare professionals.

Legal entity responsible for the study: European Cancer Patient Coalition

Funding: Baxter and Helsinn

Disclosure: All authors have declared no conflicts of interest.

1451P Breast cancer specific survival (BCSS) in young women <40 years with node negative luminal breast cancer (BC) treated based on tumor gene expression

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Background: BC at a young age is generally associated with poor prognosis, more aggressive treatment, long-term toxicities, and unique psychosocial concerns. Little data is available on outcomes defined by molecular profiles. We characterized BCSS in female patients (pts) <40 y with node negative (N0), hormone receptor positive (HR+), HER2 negative disease who were treated based on 21-gene assay Recurrence Score (RS) result.

Methods: RS results were provided electronically to SEER (US population based cancer registries) per their linkage methods (Petkov et al, npj Breast Cancer, 2016). Eligible pts were diagnosed (Jan 2004 - Dec 2012) with N0 HR+ BC, and had no prior malignancy or multiple tumors. BCSS was analyzed for female pts <40 and ≥40 y with RS results, excluding HER2+ disease. Survival was compared using a log-rank test.

Results: 1,761 of 7,186 pts <40 y (24.5%) had RS results. The proportion of pts <40 with RS < 18, RS 18-30, and RS ≥ 31 was 47%, 42%, and 11%, respectively. 47,644 of 203,033 pts ≥40 y (23.5%) had RS results. The proportion of pts ≥40 y with RS < 18, RS 18-30, and RS ≥ 31 was 56%, 37%, and 8%, respectively. The distribution of tumor size and tumor grade was similar in younger and older pts. Reported CT use increased with increasing RS, and was higher for pts <40 y ($p < 0.001$). Continuous RS result was associated with BCSS for both <40 and ≥40 y ($p < 0.001$). 5-y BCSS with RS < 18 was excellent for 820 younger pts <40 y, even in those without reported CT use (Table). Similar results were observed for ages <30 y (n = 120), 30-34 y (n = 411), and 35-39 y (n = 1,230).

Conclusions: This large population-based study of N0 HR+ HER2- BC indicates not all young women have aggressive tumor biology and poor prognosis. Nearly half (47%) of women <40 y have RS < 18 and favorable 5-y BCSS with limited CT use. An important minority (11%) with high RS have worse outcomes despite CT. Longer term follow-up is planned.

Legal entity responsible for the study: National Cancer Institute

Funding: National Cancer Institute

Disclosure: S. Shak: Full-time employee of Genomic Health and a shareholder of Genomic Health. D. Miller: Employee of Genomic Health. All other authors have declared no conflicts of interest.

1452P Risk of malignant mesothelioma in Spain from environmental asbestos exposure

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Background: The link between malignant mesothelioma (MM), and asbestos exposure (AE), is very high. AE may have occupational or environmental non-occupational source. The highest levels of AE occur in the workplace and mainly affect men. However, environmental AE, affect men and women equally. As the occupational AE prevails over the environmental non-occupational, a sex-ratio < 2 alert of possible environmental AE. The objective of this study is to evaluate the spatio-temporal distribution of the sex-ratio, in order to identify those areas with possibly higher environmental AE.

Methods: We conducted an analysis of the 6,143,124 deaths in Spain during the period 2000–2015, looking for those deaths caused by MM. Information regarding sex, year of death, age at death, province, and cause of death (ICD-10) was extracted from the deceased registry of the National Institute of Statistics. We calculated the sex-ratio between the deceased by MM according to its distribution by provinces and years, and the ratio of mortality rates adjusted for age (European standard population). We also obtained the proportion of MM among the total deceased (MM per 10,000 deaths).

Results: MM deaths were 5,345. Men 4,025 and women 1,329 (sex-ratio: 3.31). During the 2000- 2015 period the sex-ratio remained relatively stable, ranging from 2.21 in 2007 to 4.31 in 2005. In the years 2000 and 2015 the sex-ratio was 3.34 and 3.07, respectively. Likewise, in the years 2000 y 2015 the men/women age-adjusted rates was 2.83 and 3.93, respectively. The variations by provinces were more pronounced. The lowest sex-ratio (1.5) corresponded to the 140 deaths of Navarra and the highest (12.67), to the 41 deaths of Vitoria. Other low sex-ratio values were detected for Almeria (2,07), Donostia (2,02), Huesca (2) and Tarragona (1,97). Among these provinces with a possible higher environmental AE risk (sex-ratio equal to or < 2.07), Donostia and Navarra have a high MM mortality (more of 13/10,000 deaths), but the other have a low or medium mortality.

Conclusions: The high provincial variability in Spain of the proportion of women who died of MM, makes necessary the carry out of new research focused in the provinces detected as with a possible greater risk of environmental asbestos exposure in the general population.

Legal entity responsible for the study: Jose Miguel Sanz-Anquela; Junior Smith Torres-Roman

Funding: None

Disclosure: J.M. Sanz-Anquela: Occasionally has served as a consultant to the court, always at the request of plaintiff asbestos victims. All other authors have declared no conflicts of interest.

1453P Tobacco exposure and adverse pathological features in oral cancer: Does age impact survival?

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Background: The role of tobacco in oral cancer is well established, however there is a wide variation in the incidence of tobacco - related oral cancer in the literature, ranging between 70-90%. Our data shows that only half of the patients with oral cancer have any history of tobacco exposure (smoking, chewing or others). Younger patients with oral cancer (<50 years) are being shown to be a distinct subset of patients, with more aggressive disease, possibly due to an underlying immunological basis. No previous literature has shown if the effect of tobacco exposure is similar in all age groups.

Table: 1451P

	RS < 18			RS 18-30			RS ≥ 31		
	N	CT (%)	5-y BCSS (95% CI)	N	CT (%)	5-y BCSS (95% CI)	N	CT (%)	5-y BCSS (95% CI)
All Pts (N = 49405)	27308	7%	99.6% (99.4%,99.7%)	18268	35%	98.7% (98.5%,98.9%)	3829	70%	95.4% (94.4%,96.2%)
<40 y (N = 1761)	820	17%	100.0% (100.0%,100.0%)	744	56%	99.8% (98.8%,100.0%)	197	80%	93.8% (85.9%,97.3%)
≥40 y (N = 47644)	26488	6%	99.5% (99.4%, 99.6%)	17524	34%	98.7% (98.4%, 98.9%)	3632	70%	95.5% (94.4%,96.3%)

Methods: From a prospectively maintained database of patients treated for oral cancer in our institution, we extracted details for 643 patients of oral cavity squamous cell carcinoma. We divided these patients into four groups, younger patients (<55 years) with or without tobacco exposure and older patients (≥55 years) with or without tobacco exposure and compared the effect of any tobacco exposure on prognostically relevant variables (like diameter, depth of invasion, extranodal extension). We also compared the progression free survival (PFS) and overall survival (OS) between those with and without tobacco exposure in each age group separately.

Results: The percentage of those with tobacco exposure was comparable in both age groups. Tobacco exposure correlated with tumour thickness ($p = 0.001$), perineural invasion ($p = 0.002$), lymphovascular invasion ($p = 0.004$) and local recurrence ($p = 0.006$) in the younger patients but not in the older patients. In younger patients, those with tobacco exposure also had a positive trend for poorer differentiation ($p = 0.07$) and extranodal extension ($p = 0.06$). Patients <55 years who had a history of tobacco exposure, had a significantly worse PFS and OS ($p = 0.03$). In patients ≥55 years, the PFS and OS between the cohorts with and without tobacco exposure was comparable ($p = 0.10$).

Conclusions: Younger patients with exposure to tobacco have worse clinical outcome, possibly as a result of adverse pathological features like perineural invasion and lymphovascular invasion. Whether this relationship is due to an underlying immune mechanism requires further study. Younger tobacco users with oral cancer are more likely to have a poor prognosis.

Legal entity responsible for the study: Amrita Institute of Medical Sciences, Kochi, India

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1455P Initiation of systemic anti-cancer treatment in the inpatient setting in a tertiary hospital in London

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Background: The landscape of adult medical oncology care has shifted across the past three decades from the hospital to the outpatient setting, reflecting factors such as patient preference, technological advancements in the delivery of therapeutics, and cost-effectiveness. There are no recent guidelines to indicate when systemic treatment should be initiated as an inpatient. This clearly presents difficulties, particularly since inpatients are associated with a poorer performance status.

Methods: We retrospectively generated data of patients at the Royal Free Hospital commencing cycle 1 of chemotherapy as an inpatient, with a particular focus on 30-day mortality, overall survival, performance status recorded prior to initiation, treatment dose and line of therapy. Data was collected over a period of 24 months from January 2015 to December 2016.

Results: We identified 34 patients across a range of tumour types and with varying performance status who fulfilled our criteria The median age of patients treated was 54.5 years. Of these, the 76% (26/34) were administered full dose therapy, with 17.6% given a 25% dose reduction, and 5.8% given with a 50% dose reduction. Of the 34 cases, 76% (26/34) were first line therapy. The treatment intent in all cases was palliative, except one case where the intent was neoadjuvant. There was a positive correlation between performance status, full-dose therapy, and first line therapy with survival (Table 1). The outcomes of inpatients were significantly worse than outpatients. 7 of 34 in our cohort died with 30 days (20.5%), while only 38.3% of them were alive at 6 months. This is compared to the overall 30-day mortality rate of our department at 2.9%.

Table: 1455P Correlation between PS, line of therapy and dose of therapy with survival (days)

Performance Status	Medial Survival (Days)
0	200
1	101.5
2	61
3	64
Line of Therapy	Median Survival (Days)
1st line	107.5
2nd line	68
3rd line	12
Dose of Therapy	Median Survival (Days)
Full Dose	110
80%	46
75%	24
50%	38

Conclusions: 1) Inpatients commenced on systemic treatment are associated with poorer overall survival compared with outpatients. 2) We would suggest adherence to the new '2016 UK CQUIN: Optimising Palliative Chemotherapy Decision Making', which recommends peer discussion within the MDT when o chemotherapy is commenced or continued when PS is greater or equal to 2 o decisions regarding commencement of 2nd line treatment or beyond are required, when there is outright progression through the first cycle of chemotherapy.

Legal entity responsible for the study: Oncology Department, Royal Free Hospital, London

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1456P Young-age onset colorectal cancer: Analysis of incidence, clinical features and outcomes

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Background: Recent studies suggest an increase in the incidence of colorectal cancer (CRC) in young-age patients. Data concerning clinical behavior, pathologic findings and prognosis are still poorly understood for this age group. The aim of this study is to analyze clinical features and survival of the young-onset CRC population in our institution.

Methods: We retrospectively reviewed records of 5,806 patients diagnosed with CRC between January/2011 and November/2016 in *Instituto do Câncer do Estado de São Paulo* and identified 781 patients aged 50 years or younger Kaplan-Meier method was used to estimate overall survival (OS) and uni/multivariate analysis were carried out to identify factors associated with OS.

Results: We found an absolute increase in the incidence of CRC in patients < 50 years by 1.88% to 2.23% annually (2011-2012: 11.6%; 2013-2014: 13.5%; 2015-2016: 15.7%) with a relative increase of 35.3% between 2011 and 2016. Median age was 42 years (17-49), 57.4% were female and 20.9% reported family history (FH) of CRC. Mismatch repair (MMR) protein immunohistochemical analysis were performed in 466 patients and 78 (16.7%) had MMR deficient CRC. Left-sided tumors were more frequent (left colon 8.2%, sigmoid 33.7% and rectum 31.5%), whereas the incidence of right-sided tumors was 19.4%. Almost all of patients were symptomatic (93.9%) and abdominal pain (39.6%) and rectal bleeding (28.7%) were common. MMR deficiency was associated with better OS ($p = 0.029$). The stage distribution was stage I 2.6%, II 25.8%, III 34.1% and IV 37.5%. The median OS of stage IV was 25 months (CI95% 20.7-29.3) and not reached for I-III ($p < 0.001$). FH of CCR ($p = 0.021$) and adjuvant chemotherapy ($p < 0.001$) were independently associated with better OS in stage IV. For stages I-III, wild-type KRAS ($p = 0.003$), FH of CCR ($p = 0.024$) and absence of lymphovascular invasion ($p < 0.001$) were associated with better OS.

Conclusions: In our experience, the incidence of early-onset CRC is increasing. Young patients were more likely to be diagnosed with metastatic disease, left-sided/rectum site and symptoms at presentation. These findings highlight the emerging importance of young-age onset CRC and the need to discuss strategies to early diagnosis.

Legal entity responsible for the study: Instituto do Câncer do Estado de São Paulo

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1457P Improved provision of written information on metastatic spinal cord compression to at-risk cancer patients at a tertiary referral centre

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Background: Metastatic spinal cord compression (MSCC) affects up to 10% of patients with disseminated malignancies, and early diagnosis correlates with improved clinical outcomes. Up to 85% of patients who present with MSCC already have motor deficit by the time of presentation. We investigated our Trust's compliance with national guidelines on providing at-risk patients with written information on the signs and symptoms of MSCC. Following a period of educational intervention we re-audited our practice.

Methods: All Oncology doctors and Specialist Nurses at the Royal Free Hospital were completed an online survey on their knowledge of national guidelines and their clinical practice. We delivered an educational intervention (including formal teaching and presentation at Departmental meetings, case discussions and providing patient information leaflets to clinicians) and re-audited our practice after 3 months.

Results: There were 29 and 20 respondents to the baseline and repeat surveys respectively. 57% vs 84% reported being moderately or very familiar with the MSCC guidelines; 32% vs 47% reported knowing where the information leaflets were kept; 3% vs 15% reported providing written information on MSCC to at risk patients at least every month. (baseline and repeat surveys, respectively)

There was a consensus amongst the clinicians that patients with spinal metastases should be considered at "highest risk", and verbal information about the risks of MSCC was most commonly given to this group. There was a 42% increase in the proportion of respondents who provided written information on the risk of MSCC to patients with spinal metastases (19 vs 61%) following the intervention.

Conclusions: 1) Provision of written patient information leaflets, formal education sessions and case discussions with clinicians resulted in increased knowledge of guidelines on MSCC at 3 months, and positive changes in clinical practice. 2) There was a significant increase in the provision of written information to the highest risk patient groups (19 to 61%). 3) By increasing patient awareness, we can increase the proportion of early self-presentations and diagnosis. This will lead to prompt intervention and improvement of neurological outcomes.

Legal entity responsible for the study: Oncology Department, Royal Free Hospital NHS Foundation Trust

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1458P Impact of mastectomy on the social well-being and family dynamics of breast cancer female patients in the Gaza Strip

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Background: The impact of mastectomy on social well-being (SWB) and family dynamics (FD) may involve the individual, social role and perception of the usefulness of social and family support affects. The purpose of the current study is to identify that impact and its related implications on SWB and FD.

Methods: This was a cross-sectional study in which a total of 173 female patients who had mastectomy in GS hospitals completed a face-to-face questionnaire designed by the researchers; which contains 3 sections including: socio-demographic data, SWB and FD. All measures utilized a five-point Likert-type scale ranging from 1 (worst outcome) to 5 (best outcome). The study was conducted at European Gaza Hospital ($n = 60$) and Alshifaa Hopsital ($n = 113$) in the GS from August 2015 to September 2016. The data was analyzed using SPSS software.

Results: Among 173 female patients, the mean age was 51 years $\pm$ 10. About 91% were unemployed, 52% had low income and 73% were of low educational level. The overall SWB score was negatively affected by 44.2% (mean score= 2.21 $\pm$ 1.33). Seventy percent of patients had a financial impact and decreased home activities. Interestingly, 57.8% claimed that involvement in family activities was not affected after mastectomy. Shockingly, 95.4% of women worried of getting divorced due to their illness. The overall impact on FD is estimated to be by 49.2% (mean score= 2.46 $\pm$ 1.64). Surprisingly, the diagnosis of BC had an impact on sexual performance in 27.1% compared to 19.1% after mastectomy.

Conclusions: Improving patients' quality of life should be one of the primary goals of BC treatment. Involving patient's family in the process of medical care may promote their SWB and FD. However, the great fear of divorce found in this study, demonstrates the insecurity of women within the society of Gaza and is possibly an expression of the lack of security in the Gaza-Strip. Assessing and addressing the SWB and FD among BC patients may enhance providing a holistic medical care and further research in the future can help in implementing this.

Legal entity responsible for the study: Faculty of Medicine at the Islamic University of Gaza, Gaza-Strip, Palestine.

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1459P Cancer incidence and mortality trends in Crete, Greece during the last two decades (1992-2013): Results from the cancer registry of Crete

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Background: Cancer registration is the systematic collection of data about cancer and tumor diseases and is a valuable tool for understanding what causes cancer and how best to diagnose and treat it. In Greece, this data collection is managed only in the island of Crete, by the Cancer Registry of Crete (CRC;) . In this study, we present data on the cancer incidence and mortality for all neoplasms in Crete, during 1992-2013. Secondary objectives were to map the longitudinal trends of all MN and per type.

Methods: Data were obtained from the Cancer Registry of Crete which is the only population-based registry in Greece since 1992 (permanent residents=623.000). Data were coded according to the ICD-10O and included several parameters on demographics, medical history, and lifestyle factors. Age-standardized incidence/mortality/100,000/year (ASIR, ASMR) were estimated, while Bayesian models were performed to assess any longitudinal variations ($a = 0.05$).

Results: ASIR and ASMR for all cancers in Crete were 302.8 and 150.5 respectively. Cancer of the lung and bronchus is the most common invasive cancer and cause of cancer mortality in males and females (40.2 new cases/100,000/year and 36.5 deaths/100,000/year). Colorectal cancer accounted for 25.1 new cases/100,000/year and 14.7 deaths/100,000/year, and breast cancer for 28.6 new cases/100,000/year and 11.1 deaths/100,000/year. The invasive neoplasms that presented the greatest statistically significant increasing trends during the past 22 years were: lung and bronchus (in women), colorectal cancer (in both sexes), cervical cancer, leukemia (in men) and thyroid cancer (in both sexes).

Conclusions: Although the Cretan cancer rates are still lower than the mean European ones, significant increasing trends were identified; indicating the urgency for clinical and public health measures. Since the cancers that account the most in this increase are preventable by smoking cessation, screening, and vaccination. High priority should be given to the development of population-based interventions.

Legal entity responsible for the study: University of Crete

Funding: Region of Crete

Disclosure: All authors have declared no conflicts of interest.

1460P Robotic anticancer drug compounding assist system for the preparation of injectable antineoplastic drugs

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Background: Many antineoplastic drugs are known to be mutagenic or teratogenic. Medical personnel handling antineoplastic drugs are at a high risk of occupational exposure. Therefore, in collaboration with Yaskawa Electric Corporation and Nikka Micron Co., Ltd, we developed the Cancer Drug Compounding Assist System (CDCAS). The CDCAS is an automated robotic system designed to efficiently facilitate the accurate preparation of drugs based on dose. In this study, we evaluated the CDCAS for accuracy, site contamination, and washing performance in the preparation of antineoplastic drugs.

Methods: 5-Fluorouracil (5-FU; 600, 800, or 1200 mg) was added to 100 mL of saline; 5 samples of each formulation were prepared. The weight of the mixed drugs prepared using the CDCAS was compared to those prepared by a pharmacist, and the accuracy of each preparation was calculated in terms of percentage relative error. The acceptable variance was set at $\pm$ 5%. To test for contamination, cyclophosphamide (800 mg) was continuously added to 50 bags of 100 mL saline solution. Then, 25 locations inside the isolator were identified for measurement. Cyclophosphamide was collected from those sites by using a sampling sheet method. Twenty of those samples revealed adherence of 5-FU (300 μL) to the infusion bag surface. Ozonated water was used to wash 5-FU from the surface of the infusion bags. After the washing process, any 5-FU remaining on the infusion bag surface was recovered via a wiping method.

Results: The average weight error ratio for the CDCAS and the pharmacist was −0.62% and 2.69%, respectively. Contamination of cyclophosphamide was confirmed at eight sites. Pollution of 5-FU was confirmed for two samples, and the removal rate was $\geq$ 99.9%.

Conclusions: Our study demonstrated that the CDCAS's preparation accuracy and cleaning performance are within acceptable limits. Thus, the CDCAS could be used to potentially reduce occupational exposure to antineoplastic drugs.

Legal entity responsible for the study: Satohiro Masuda

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1461P Monitoring of contamination with cytostatics in pharmacies and hospitals in the Czech Republic

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Background: Monitoring of contamination with cytostatics was introduced in practice in the Czech Republic by CYTO project managed by the pharmacy of Masaryk Memorial Cancer Institute (MMI) in years 2006-2010. The number of prescriptions of cytostatic drugs increased within the Czech Republic from 23000 bags and syringes in 2010 up to 38000 in 2015. So as to set up standards for the protection of healthcare professionals, it is necessary to monitor contamination regularly at all work sites engaged in compounding or administration - both in the pharmacy (Pharm) and at the hospital departments (HD)/stationaries (S). We have introduced the monitoring of cyclophosphamide (CP) and Pt cytostatics (Pt) to routine practice in 2007. In 2015, there was also implemented monitoring of 5-fluorouracil (FU). These drugs belong to the most frequently used cytostatics in MMI (49.0% of compounded units).

Methods: The samples for detection of contamination of surfaces were collected with a nonwoven swab. CP and FU were assessed with HPLC with TQ-S MS, with limits of detection 1.1pg.cm^{-2} for CP und 7 pg.cm^{-2} for FU. Pt cytostatics were analyzed by MS with inductively coupled plasma proving LOD 0.7 pg.cm^{-2}.

Results: Maximal levels of FU detected on floors were: 775 pg.cm^{-2} at HD, 564 pg.cm^{-2} in P, at compounding units and 25 pg.cm^{-2} in P, in storage rooms. Similarly, maximal detected levels of CP on floors were found at the HD: 3244 pg.cm^{-2}, 638 pg.cm^{-2} in the P, compounding units and 235 pg.cm^{-2} in P, in the storage rooms. Maximal detected levels of Pt on floors was again found in the HD, with levels of 5390 pg.cm^{-2}, then 84 pg.cm^{-2} in P, compounding units, and 57 pg.cm^{-2} in P, in the storage rooms.

Conclusions: According to our findings, hospital pharmacists are able to decrease the contamination on their workplaces. On the other hand, improvement is needed at the hospital departments and stationaries, where hospital pharmacists may co-operate on setting the safety standards.

Legal entity responsible for the study: Masaryk Memorial Cancer Institute

Funding: Masaryk Memorial Cancer Institute

Disclosure: All authors have declared no conflicts of interest.

1462P New treatments in Oncology: Clinical practice regarding the management of Adverse Events (AEs). Results from a survey conducted by the Hellenic Group of Young Oncologists (HeGYO)

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Background: Targeted therapies with distinct toxicities have revolutionized treatment of advanced cancer. Aim of this study was to assess patterns of practice for the management of these AEs, which can impair patient's(pts) quality of life and hamper compliance, potentially leading to treatment failure.

Methods: Between March 2017 and May 2017, an online questionnaire was distributed by HeGYO to oncologists to provide their answers anonymously.

Results: 79 oncologists participated in the survey. The majority were medical oncologists (80%), 18% were clinical/radiation oncologists and 2% haematologists oncologists. Of them, 30% were in specialty training and 72% were ESMO members. Although 64.6% stated that they are very familiar with the new treatments in oncology, the majority (67.1%) spend less than 30% of their treatment initiation visit to inform pts on AEs. Only a minority (29.1%) gives diaries to pts for self reporting of AEs, but 59.4% offers educational material and 89.8% reaches proactively to pts. 53.2% do not make follow up phone calls between scheduled visits, while 58.2% report that there is not a call center service available in their institution for the pts to report AEs. More than 80% of oncologists described their practice to treat toxicities as more guideline-based than empiric and 92.4% of them were keen to refer pts to other medical specialties to optimize management of toxicities. 60.8% reported that a dose reduction or discontinuation was necessary in 10-30% of their pts and 59.5% reported that at least 1 of their pts discontinued treatment without informing them. Time constraints and the chaotic nature of web information were the predominant barriers interfering with doctor's education.

Conclusions: This survey emphasizes the unmet need for continuous education among health professionals and pts and effective multidisciplinary collaboration for the optimization of AEs management. The majority of participants acknowledged the importance of informing their pts and treating their side effects according to guidelines. However, they describe significant obstacles in their daily practice.

Legal entity responsible for the study: Hellenic Group of Young Oncologists (HeGYO), under the auspices of the Hellenic Society of Medical Oncology (HeSMO)

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1463P Oncologists' perspectives on biologic substitution

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Background: Biosimilars are similar but not identical to originator biologics. As more biosimilars are approved, pharmacy or hospital-level substitution of biologics is becoming more common, potentially excluding physicians from decisions regarding the treatment of their patients.

Methods: The Alliance for Safe Biologic Medicines (ASBM) conducted regional, 15-minute web-based surveys among biologics prescribers around the world to determine their opinions on biologic substitution. Prescribers were asked to rate: (1) the importance of authority to decide the most suitable biologic for their patients, (2) the importance of designating a biologic as "dispense as written" (DAW, or equivalent), (3) the acceptability of biologic substitution, and (4) the importance of notification of biologic substitution.

Results: A total of 1,856 responses were received: 470 (25%) Europe, 427 (23%) Canada, 400 (22%) US, 399 (21%) Latin America, and 160 (8.6%) Australia. Across regions, most prescribers were from the hospital setting, and most had $\geq$ 11 years in practice. Between 10% and 25% of prescribers were oncologists (16% Europe, 10% Canada, 16% US, 18% Latin America, and 25% Australia). Across regions, most oncologists (75%) feel that it is critically/very important to have sole decision-making authority regarding the suitability of a biologic, and 71% that it is critically/very important to have DAW authority. Only 6% of oncologists feel that pharmacy-level substitution is totally acceptable; 58% consider switching to a biosimilar unacceptable, and 36% consider switching acceptable provided it has been agreed to in advance. Most (76%) also feel that it is critically/very important to be notified of pharmacy-level substitution. Responses were mostly aligned across regions; however, one notable difference was the relatively low percentage of Australian oncologists (23% vs 58% overall) who feel that substitution is unacceptable.

Conclusions: Our survey indicates that most oncologists believe it is important for them to be able to control which biologic—original product vs biosimilar—they prescribe for their patients. This is likely to become increasingly important with the availability of biosimilars used for curative intent.

Legal entity responsible for the study: Alliance for Safe Biologic Medicines

Funding: Amgen and AbbVie

Disclosure: M. Reilly: Funding from Amgen and AbbVie Inc.

A. Spiegel: Funding from BIO, PhRMA, Amgen, Roche, EMD Serano.

1464P Ukrainian Association for helping patients with lymphoproliferative diseases: Patients support care program

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Background: Treatment patients with cancer, including chronic lymphoproliferative diseases (CLPD), includes not only special therapy, such as surgery, chemo- and radiation therapy, as well as psychological and social support to this group of patients. With this goal, the first Ukrainian Association for helping Patients with Lymphoproliferative Diseases (UAPLPD) was founded in 2006.

Methods: 1) To cooperate with various institutions and doctors who treat patients with CLPD. 2) To create programs which promote social assistance and protection for patients with CLPD 3) To create an appropriate financial framework for solving diagnosis and treatment difficulties.

Results: Currently, there are 18 centers in 24 regions of Ukraine and 1000 members (25% of health professionals and researchers and 75% of patients and their family members) in UAPLPD. Each year, the number of association members is growing rapidly Since 2006, the association has been carrying out a lot of activities aimed to support patients, their relatives and of course, doctors. Nowadays, we have 6 ongoing projects: "Lymphoma day", "Psychological help for patients and relatives", social project with Ukrainian pop-stars "I will survive. . .", program which help to reduce prices for expensive drugs "Support patient", "Art against cancer" and "Survivors day". Within the framework of all projects, the association provides a lot of charity concerts, art exhibitions, shoot video for promo-actions, provide art-therapy, therapeutic horse riding. There are also many educational events for patients and doctors. The UAPLPD pays attention to the assistance for diagnosing and treating patients and partially allocates money for reagents purchasing, perform PET/CT scans for free to over 40 patients annually and could cover cost-effective treatment. The Association has printed out a lot of informational material such as patient brochures on nutrition, physical therapy with our patients' stories and examples. We update and edit this information annualy, including the scientific editions as well. The latter one include guidelines for diagnostic and treatment multiple myeloma, anemia, the evaluation of response after treatment in patients with lymphoma. Since 2015, a psychologist has been working for a full time at the oncohematology department.

Conclusions: The work of the Association for helping patients is very important and necessary for effective treatment and patient rehabilitation.

Legal entity responsible for the study: I. Kryachok

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1466P Feasibility and barriers to optimal oncological treatment in solid organ transplant patients with de novo cancer

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Background: Transplanted patients (tpts) display higher cancer incidence rates compared to general population. Anti-tumor treatment after transplantation remains scarcely described. This study aimed to report oncological therapy feasibility and outcome in tpts with *de novo* cancers.

Methods: We retrospectively analyzed all consecutive cases of de *novo cancer* in renal and liver tpts treated in our center. Pts were identified based on systematic research in tpts databases from 2000 to 2016. Pts presenting with non-melanic cutaneous tumors only were excluded. Clinical features, treatments, toxicity and survival data were collected. Active optimal treatment was assessed by comparing treatment that was actually administered with guidelines.

Results: Among 4637 tpts, 209 cases of *de novo* cancer were identified in 176 (3.8%) pts. Mean age was 52.5+/-11.3 at transplantation and 59+/-10.6 at cancer diagnosis; 122 (69%) were men; 96 (55%) were renal tpts and 80 (45%) liver tpts. At cancer diagnosis, performance status (PS) was 0-1 in 89% (n = 142/160). Tumor type was mainly epithelial (75%, n = 150/200); tumor stage was localized in 80% (n = 163/205) and advanced in 20% (n = 42/205) . Among pts with initially localized tumors, 13% (n = 22/163) had cancer recurrence. Median overall survivals of pts with localized and advanced cancer were of 166 (CI95%: 100.3-ND) and 8.8 (CI95%: 5.0-47.2) months, respectively Among pts with localized tumors, 80% (n = 134/156) received optimal treatment. Reasons for non-optimal treatment were comorbidities in 36% (n = 8/22), risks for the transplant in 36% (n = 8/22), and/or toxicity in 36% (n = 8/22). In contrast, at advanced/recurrent stage, only 36% (n = 19/53) of pts received optimal treatment, and 28% (n = 15/53) best supportive care only. Barriers to optimal treatment were comorbidities in 19% (n = 6/32), risks for the transplant in 22% (n = 7/32), toxicities in 19% (n = 6/32), and poor PS in 33% (n = 17/32).

Conclusions: Oncological treatments are feasible in tpts and survival seems similar to general population. Concerns about the risk of toxicity for the transplanted organ and comorbidities were the main reasons for non-optimal treatment. These observations warrant confirmation in a prospective multicenter study.

Legal entity responsible for the study: CHU Henri Mondor

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1467P Generating patient reported outcome norms for an EU cancer population using real world data (FACT-G)

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Background: The main aim of this analysis was to generate population norms from an EU sample of cancer patients for the FACT-G instrument using real world data. Comparisons were made between existing norms based on a US population and the newly developed EU norms.

Methods: Data was collected through the Adelphi Real World Disease-Specific Programmes (DSPs) across breast, gastric, melanoma, non-small cell lung and prostate cancers. Cross-sectional surveys were administered to physicians and patients between January 2015 and March 2017, resulting in a total sample of 4899 patients. The US population norms outlined by Brucker et al. (Evaluation & the Health Professions. 2005;28(2):192-211) are commonly used to aid interpretation of FACT-G scores but there are no large sample norms specifically derived for the EU population. Analysis included checking internal reliability of the FACT-G sub-scales in the EU sample and comparisons between the EU and existing US population norms using minimum important differences (MIDs) of 3 points for FACT-G sub-scales and 7 points for total FACT-G score (Yost et al. Evaluation & the Health Professions. 2005;28(2):172-191).

Results: The EU sample had similar population characteristics to the US sample with respect to age, gender and ECOG status but consisted of a wider sample of cancer types (including haematological cancers). Internal consistency was met ($\alpha > 0.7$) for all subscales within the FACT-G for the EU population. Comparisons between the population norms indicate differences in FACT-G scores between the EU and US samples based on MIDs. Differences exceeding MIDs were noted across social well-being (SWB), emotional well-being (EWB), functional well-being (FWB) and overall FACT-G, but not for physical well-being (PWB). Further analysis was undertaken to explore differences by gender.

Table: 1467P

	SWB	EWB	FWB	PWB	FACT-G
EU mean score	17.4	13.3	12.3	18.5	61.5
US mean score	22.1	18.7	18.9	21.3	80.9
Population difference	4.7*	5.4*	6.6*	2.8	19.4*

*Indicates MID exceeded.

Conclusions: Differences highlighted between FACT-G scores for the EU and US cancer populations indicate that population norms may be region-specific or specific to cancer type. The resulting EU population norms can be used to aid interpretation of FACT-G scores across a range of cancer types.

Legal entity responsible for the study: Adelphi Real World

Funding: None

Disclosure: A. Rider, S. Simpson, B. Bennett, K. Byrne, P. Hallworth, T. Desai, K. Cocks: Employee of Adelphi Group.

1468P Development of a web-based application using machine learning algorithms to facilitate systematic literature reviews

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Background: Systematic review is an important element of medical research but rapid proliferation of published literature presents challenges to manual review. Computer science advances can improve workload by using algorithms to automatically select and extract data from articles. We initiated a systematic review of phase I immunotherapy clinical trials and used natural language processing to aid article screening.

Methods: A literature search was performed across MEDLINE, Embase and CENTRAL in September 2016 using 100+ search terms in the categories "neoplasm", "immunotherapy" and "phase I clinical trial". Only English language studies published since 1990 were included. We developed a web-based interface that allowed human reviewers to apply inclusion/exclusion labels based on title and abstract screening. Articles were screened by two independent reviewers who were blinded to results. An article similarity based algorithm using weighted logistic regression to predict "include" and "exclude" labels is being trained and herein we report interim results.

Results: 28,235 articles were identified from the literature search; 19,000 remained after duplicates and conference abstracts were excluded. 4,034 (21.2%) were screened, of which 532 (13.2%) were labeled "include" by at least one reviewer. 1,944 (10.2%) were screened by two reviewers with concordance of 93.7%. The prediction algorithm was weighted to improve the detection of "include" labels, and achieved 80.6% sensitivity and 78.2% specificity when compared to manual review results. The positive and negative predictive values were 34.4% and 96.6%, respectively.

Conclusions: A machine learning algorithm trained on manual reviews was able to predict systematic review article inclusion with approximately 80% accuracy. Algorithm performance was affected by the low rate of included articles, but irrelevant articles were able to be excluded with high confidence. Further development is ongoing to optimize the algorithm to improve sensitivity. Once optimized, this innovative machine learning process could transform the conduct of systematic reviews.

Legal entity responsible for the study: N/A

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1469P Survival patterns for different types of cancers in the United States (1973-2012)

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Background: Most studies addressing survival patterns focus on 5-years survival data due to difficulties in long-term patients' follow up. The aim of this study was to explore data on survival making use of the main advantage of SEER (National Cancer Institute Surveillance, Epidemiology, and End Results) program; that is long-term follow up of patients' records. This enabled reporting 5-years relative survival, 10-years relative

Table: 1469P showing relative survival data as a function of time and tumor type

	1973-1982	1983-1992	1993-2002	2003-2012	1973-2012
All Cases					
5-Year RS	51%	57.8%	65.7%	68.9%	64.6%
10-Year RS	43.6%	51.1%	60.5%	63.7%	58.7%
20-Year RS	36.9%	44.4%	54.1%		51.4%
Solid Malignancies					
5-Year RS	51.8%	58.7%	66.6%	69.2%	65.2%
10-Year RS	44.8%	52.4%	61.8%	64.4%	59.7%
20-Year RS	38.3%	46%	55.6%		52.7%
Hematological Malignancies					
5-Year RS	42.4%	48.4%	56.2%	65.5%	58.1%
10-Year RS	30.9%	37.5%	47.5%	56.6%	48%
20-Year RS	22.7%	29.4%	38.6%		37.9%

survival, and 20-years relative survival for different types of cancers. Survival trends as a function of time and tumor types were also provided.

Methods: SEER*Stat version 8.3.4 was used for data acquisition and analysis, where (SEER 18 Regs Nov 2015 Submission) database was used as the data source. Only cases diagnosed between 1973-2012 with malignant behavior, known age, and microscopic confirmation were included. Relative survival was calculated using Ederer II method. Tumors were classified according to ICD-O-3 into either solid malignancies (8000/3-9581/3) or hematological malignancies (9590/3+).

Results: Cancer cases diagnosed between 1973 and 2012 showed a 5-years relative survival of 64.6% (CI: 64.5%-64.6%), a 10-year relative survival of 58.7% (CI: 58.6%-58.7%), and a 20-years relative survival of 51.4% (CI:51.3%-51.5%). All of these percentages were much higher with solid malignancies than hematological ones [Table].

Conclusions: Long-term follow up data were suggestive of 20-years relative survival of 51.4% for all cancers. Data were also suggestive of improved relative survival over time. Unexpectedly, hematological malignancies, despite most of them being thought of as curable ones, appeared to have lower relative survival than solid tumors.

Legal entity responsible for the study: Mohamed Alaa Gouda

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1470P Decisions and supports around clinical trial participation: A national study by Cancer Trials Ireland

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Background: We conducted a national survey of cancer patients (pts) to determine what factors influence their decision to participate in a cancer clinical trial (CCT) and what supports they use(d).

Methods: Pts with a diagnosis of malignancy, $\geq$ 18 years, able to provide informed consent and complete a questionnaire independently were eligible. Questionnaires were administered to pts attending 14 cancer centres from 22nd April to Nov 23rd 2016.

Results: 1,090 pts completed the questionnaire (386 (35.6%) men and 697(64.4%) women). Median age was 60 years (IQR 50-69). 311 (29.5%) had previously been offered a CCT and 303 pts had participated. Factors most frequently ranked as important regarding decisions about CCT participation included; chance to advance research (n = 846, 81.0%); living longer/feeling better (n = 851, 81.5%); recommendation by cancer doctor (n = 797, 76.3%); closer monitoring (n = 528, 50.5%); fear of more side-effects (381,36.5%) or death (n = 337,32.3%); concerns about the treatment not working (n = 446,42.7%); increased hospital visits (n = 292, 28.0%); age (n = 355, 34.0%). Only 83 pts (9.3%) independently asked about participating in a CCT. Pts were asked about hypothetical participation in a CCT of a new drug that appeared safe but which could be better than/similar to/or worse than standard treatment (ST). 687 (65%) pts reported they would consider participation but more than half 336 (51.1%) of those re-considered when a subsequent question re-stated the possibility the study drug could be worse than ST. Of those previously offered a CCT most (n = 214, 68.8%) had decided without help. When making decisions about CCT participation; family (n = 175, 56.2%), internet (n = 67, 21.5%) and GP (n = 48, 15.4%) were frequent sources of support. Most sources encouraged (n = 169, 54.3%) or were neutral about participation (n = 72, 23.2%). Cancer doctors and specialist nurses scored highest in terms of pts' trust about CCT information; 250 (69.8%) and 196 (59.4%) pts gave them full scores respectively.

Conclusions: Decisions about CCT's are complex, based on personal and altruistic factors and may be influenced by the type and detail of information given and by who provides it. Few pts we surveyed asked about a CCT, but most who had been offered a CCT had participated.

Legal entity responsible for the study: Catherine M. Kelly

Funding: Cancer Trials Ireland with funding from Abbvie, Bayor, Amgen and Inveva for this project

Disclosure: All authors have declared no conflicts of interest.

1471P Academic clinical research: Enough players to get out there?

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Background: The European Regulation 536/2014 definitively establishes the equality between pharma-sponsored and academic clinical research, raising the bar of standards for no profit trials. Italy has always been known for the quality of its studies: our researchers have produced the 3.9% of world scientific papers in 2015-16 and 44 were among the 2016 world's most influential scientific minds. However, the new compelling rules imposed by law make these great minds lacking in the absence of well-arranged staff, with dedicated professionals as clinical research coordinators (CRCs). Unfortunately, the national collective health contracts allow the employment of these experts only through atypical contracts that, due to new government requirements, will

soon be banned. We have decided to map how much the problem was widespread among Italian CRCs.

Methods: In November 2016 a web survey, focused on the imminent contracts' expiration problem, has been sent to about 300 CRCs.

Results: Our survey was completed by 231 CRCs (77%). The majority of respondents (78%) work thanks to atypical contracts, while few can count on more stable ones (7.4% fixed term and 14.6% open-ended). Public hospitals have the more difficulties to ensure stable employment: only 25% of permanent contracts come from this type of structures and purely thanks to loopholes; indeed, despite their educational background, CRCs are employed almost exclusively as non-qualified administrative personnel. The 67.5% of respondents will be affected by the contract problem, with multiple expiration timing: 32% Jan-Apr 17; 23% May-Aug 17; 23% Sep-Dec 17; 17.3% from Jan 18. Interestingly, about 50 CRCs were unwilling to participate, demoralized from the age-issue of the lack of professional recognition.

Conclusions: The need for clinical trials units officially and contractually recognized by competent authorities is a priority. The new government dispositions about atypical contracts could create a vacuum of skilled work force, which can hardly be covered by physicians. Since data are understated and the problem also affects another "big ghost" of clinical research (study nurse), in the absence of a permanent solution, Italy is unlikely to meet the required standards with a loss of appealing, but mostly with a slump of therapeutic options.

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ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

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SARCOMA

1473O Encouraging activity of novel pan-KIT and PDGFRα inhibitor DCC-2618 in patients (pts) with Gastrointestinal Stromal Tumor (GIST)

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Background: Approved TKIs primarily inhibit either the KIT ATP binding pocket (exon 13/14) or a subset of activation loop mutations (exon 17/18) and do not demonstrate activity across both regions known to cause imatinib resistance in GIST. This leaves significant liabilities in inhibitory coverage of known KIT resistance mutations. DCC-2618 is a potent kinase switch control inhibitor active across a broad range of mutations which emerge on treatment with approved TKIs.

Methods: This is a dose-escalation study of oral DCC-2618 (QD or BID q28 days) followed by an expansion cohort in pre-treated TKI resistant GIST. During the escalation phase, FDG-PET scans were performed at baseline and after 3 wks of therapy; CT scans every 2 cycles. Next generation sequencing (NGS) of plasma cell-free (cf) DNA was performed throughout the study to quantify KIT, PDGFRa and other molecular alterations. Concordance of mutational status between plasma cfDNA and tumor tissue was assessed.

Results: 33/42 pts enrolled had KIT (30) or PDGFRa- (3) driven GIST and received daily doses ranging from 40-400 mg. Mean prior lines of therapy was 4.8. The dose selected for expansion was 150 mg QD. Safety for all 42 pts was as follows: grade (G) 3/4 adverse effects (regardless of attribution, occurring in > 1 pt) included anemia (15), asymptomatic lipase increase () (7), hypertension (4), creatine phosphokinase (CPK) (2), lower GI hemorrhage (2). Two of the G3/4 lipase at 100 mg BID and 200 mg BID and one CPK at 150 mg QD were DLTs. Of 19 pts with KIT mutant GIST assessed by FDG PET, 15 (79%) had a partial metabolic response per EORTC criteria. 2 out of 23 evaluable patients showed RECIST partial responses (PRs) and 6 out of 11 evaluable patients at doses of ^{3}100 mg/d had RECIST progression free survival of > 6 months (5 pts on therapy at ^{3}Cycle 10). NGS of plasma cfDNA revealed a reduction of mutation allele frequency (MAF) in exons 9, 11, 13, 14, 17 and 18.

Conclusions: DCC-2618 showed encouraging disease control with objective responses and prolonged stable disease in heavily pre-treated GIST patients. The notable decreases in MAF of resistance mutations across all exons supports the use of DCC-2618 beyond imatinib resistance.

Clinical trial identification: NCT02571036

Legal entity responsible for the study: Deciphera

Funding: Deciphera

Disclosure: F. Janku: Research funding: Deciphera; Scientific Advisory Board: Deciphera. D. Flynn, M. Kaufman: Full-time employee of Deciphera Pharmaceuticals. J. Pitman, B. Smith: Full-time employee of Deciphera Pharmaceuticals, stock options at Decipher Pharmaceuticals. All other authors have declared no conflicts of interest.

1474O Improved overall and progression free survival after surgery in expert sites for sarcoma patients: A nationwide study of FSG-GETO/NETSARC

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Background: Sarcomas are rare but aggressive diseases. Specialized multidisciplinary management is not implemented for all patients in most countries. We investigated the impact of the surgery in a reference center on relapse and survival in the nationwide NETSARC/RREPS study.

Methods: NETSARC (netsarc.org) is a network of 26 reference sarcoma centers with specialized MDTB, funded by the French National Cancer Institute to improve the outcome of sarcoma patients. Since 2010, presentation to an MDTB and second pathological review are mandatory for sarcoma patients. Patients' characteristics and follow-up are collected in a database regularly monitored. Uni and multivariate analysis of prognostic factors for local relapse free survival (LRFS), relapse free survival (RFS) and overall (OS) were conducted.

Results: Out of the 9,594 non-metastatic pts aged > =15, with a first diagnosis of soft tissue and visceral sarcoma obtained between Jan 2010 and Dec 2014, 3505 (37%) and 6089 (63%) were operated within vs outside of one of the 26 NETSARC reference center. The former group had worse prognostic characteristics (age, size, grade, depth $p < 0.0001$ all). In univariate analysis, surgery within a reference center was associated with a better LRFS & RFS (median 60 vs 41 mos, and 25 vs 21 mos, respectively, logrank $p < 0.001$). LRFS and RFS were significantly better for pts operated in reference centers in all individual subgroups of quality of resection, (R0, R1, R2, R unknown) ($p < 0.001$). Surgery in reference center was an independent good prognostic factor for LRFS (HR: 0,60), RFS (HR:0,79) as well as OS (HR:0,68) using Cox model ($p < 0.001$ all).

Conclusions: In this nationwide unselected population, the LRFS and RFS of sarcoma patients is worse than that reported in expert centers series. Surgery in reference center is associated with significant reduction of the risk of relapse and death.

Legal entity responsible for the study: NetSARC/French Sarcoma Group_GETO

Funding: INCA DGOS

Disclosure: All authors have declared no conflicts of interest.

1475PD A randomized clinical trial of adjuvant chemotherapy with doxorubicin, ifosfamide and cisplatin (API), followed by radiotherapy versus radiotherapy alone in patients with localized uterine sarcomas (SARCGYN study). Update at 10 years

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Background: There is no proven benefit of adjuvant treatment in uterine sarcoma (US). SARCGYN was a phase-III study which compared adjuvant polychemotherapy followed by pelvic radiotherapy (RT) (arm A) *versus* RT alone (arm B). The study met its primary end point (3-year progression-free survival (PFS)) and showed a statistical increase of the 3-year PFS in the chemo+RT arm (A) *vs* radiation arm (B) (55% and 41% respectively, [$P = 0.048$]) after a median follow-up of 4.3 years (Ann Oncol 2013). Secondary end-point was overall survival (OS) that required a longer follow-up.

Methods: Patients with FIGO stage ≤III US, and physiological age ≤65 years were randomized after complete surgery and normal thoracic, abdominal and pelvic CT scans between CT and no CT, with a stratification between carcinosarcomas (CS) *versus* others. Study was stopped earlier because of lack of recruitment. All patients received pelvic RT (45 grays); vaginal brachytherapy was optional. Chemotherapy consisted in four cycles of doxorubicin 50 mg/m^2, d1; ifosfamide 3 g/m^2/day d1-2; cisplatin 75 mg/m^2, d3; + G-CSF q 3 weeks.

Results: Eighty-one patients were included: 39 in arm A and 42 in arm B; 52 stage I, 16 stage II, and 13 stage III; 53 leiomyosarcomas, 9 undifferenciated sarcomas, and 19 carcinosarcomas. API was toxic with two toxic deaths and one acute leukemia. After a median FU of 9.9 years [0.3-15.1], 42/81 patients relapsed, 16 in arm A, and 26 in arm B, and 38 died, 16 in arm A, and 22 in arm B. The 5-year OS is 74% in arm A and 60% in arm B, and the difference is not significant ($p = 0.16$).

Conclusions: In this trial interrupted at an early stage and with a longer follow-up, there is no statistical impact of API adjuvant CT on OS. The two toxic deaths and the integration of carcinosarcomas may have impacted on the global prognosis. A selection

of a specific uterine population and a less toxic chemotherapy for future studies are mandatory.

Clinical trial identification: NCT00162721

Legal entity responsible for the study: Institut de Cancérologie Gustave Roussy

Funding: Association pour la Recherche contre le Cancer; Chugaï Pharma

Disclosure: P. Pautier: Advisory board: Roche and Pharmamar. S. Piperno-Neumann: Travel grants PharmaMar, Novartis. F. Bertucci: Traveling grants, PharmaMar, Novartis. F. Duffaud: Consultancy work: Lilly, Pharmamar, Bayer, Novartis Travel grants: Pfizer, Pharmamar. All other authors have declared no conflicts of interest.

1476PD Tumour necrosis and clinical outcomes following neoadjuvant therapy in soft tissue sarcoma (STS)

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Background: Tumour necrosis following chemotherapy is prognostic in bone sarcoma, but remains undefined in STS.

Methods: We searched MEDLINE, MEDLINE in progress, EMBASE and Cochrane to identify studies that investigated neoadjuvant therapy in STS. Eligible studies were required to have data on survival outcomes based on tumor necrosis in the resected specimen, or provided individual patient data. Hazard ratios (HR) for relapse free (RFS) and overall survival (OS) as well as odds ratios (OR) for recurrence at 3 years and for death at 5 years were pooled in a random effect meta-analysis. Association between patient characteristics and attainment of $\geq$ 90% necrosis were explored with logistic regression.

Results: 21 studies comprising 1644 patients were included in this analysis. Location of the tumor included the extremities in the majority (n = 1459; 89%). Induction regimens included chemotherapy/radiation (n = 813; 49%), chemotherapy alone (n = 418; 25%), chemotherapy/caffeine (n = 81; 5%), radiotherapy alone (n = 78; 5%), isolated limb perfusion (ILP) with (n = 28; 2%) or without radiation (n = 208; 13%), and targeted therapy/radiotherapy (n = 18; 1%). Utilizing a cut-off of 90%, patients with $\geq$ 90% tumour necrosis had significantly reduced risk of recurrence at 3 years (OR0.30; 95% CI: 0.20-0.44; $p < 0.0001$) and had improved 5-year OS (OR 0.38; 95% CI: 0.23-0.63; $p < 0.001$). Limiting the analysis to studies with reported HR (n = 6), patients with $\geq$ 90% tumor necrosis also had a lower risk of recurrence (HR 0.68; 95% CI: 0.49-0.94; $p = 0.02$) and death (HR 0.54; 95% CI: 0.41-0.71; $p < 0.001$). There was no significant association between age, gender, and histologic subtype with attainment of $\geq$ 90% necrosis. Compared to other neoadjuvant modalities, ILP was associated with higher odds of achieving $\geq$ 90% necrosis (OR 12.1; 95% CI: 3.69-39.88; $p < 0.001$).

Conclusions: Tumour necrosis $\geq$ 90% following neoadjuvant therapy is associated with reduced recurrence risk and improved overall survival in patients with STS.

Legal entity responsible for the study: Princess Margaret Cancer Centre

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1477PD Prognosis of desmoid tumours initially managed with surveillance only at all anatomical locations

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Background: Desmoid tumours are locally aggressive mesenchymal tumours that lack metastatic potential. Tumour behaviour is unpredictable and varies along a spectrum from remission to growth. Recently, active surveillance has been increasingly adopted as initial management. The aim of this study is to analyse the need and indications for treatment in desmoid patients initially managed with surveillance only.

Methods: Patients with a desmoid tumour at any anatomical location diagnosed between 1998 and 2016 were selected from a prospectively maintained database. Differences between patient groups were analysed with independent t-tests or Chi-square tests. Inverse univariate cox proportional hazard regression analyses were conducted to assess factors associated with start of treatment, tumour behaviour and pain.

Results: A total of 168 patients initially managed with surveillance only were identified. The tumours were located in an extremity (51), in the abdominal wall (61), intra-abdominally (15), in the chest wall (30) or at other locations (11). From these patients, 33% (n = 55) developed progressive disease, 38% (n = 64) had stable disease and 28% (n = 47) had a remission. Tumours in patients <50 years old were more likely to show progressive disease after surveillance in an univariate analysis ($p = 0.046$). A total of 78 patients (46%) eventually had some form of treatment, while 90 patients (54%) continued on surveillance only. Median time to treatment was 31 months. Patients with tumours >5 cm were more likely to undergo treatment ($p < 0.01$), while no significant differences were found between the different anatomical locations. Treatment consisted mainly of surgery (n = 40, 44%) or systemic therapy (n = 36, 40%). The indications to start treatment were pain (32%), growth (31%) or both (13%). Tumours located in the chest wall or upper extremity caused significantly more pain than other locations ($p = 0.01$), while pregnancy-associated desmoid tumours caused significantly less pain ($p = 0.04$).

Conclusions: Patients with desmoid tumours can be managed with surveillance only, but a large minority still needs treatment after an initial period of surveillance. Pain and tumour growth are the most common indications to start treatment after initial surveillance.

Legal entity responsible for the study: Winette van der Graaf

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1478PD Adult Translocation-related soft tissue sarcomas (TRS): Presentation, management and outcome of 2,143 cases confirmed by expert pathologists

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Background: To better characterize the TRS patterns compared to other sarcomas.

Methods: Retrospective multicenter study of 12,262 patients treated between 01/1980 and 12/2013 in one of 22 French Referral Sarcoma Center and enrolled in the "Conticabase". Diagnoses were systematically reviewed by expert pathologists and entities classified according to the 2013 WHO Classification.

Results: The median follow-up was 4.9 years (95%-CI: 4.7-5.0). TRS included 13 entities: synovial S (760 cases; 7.4%/5-y OS: 64%), myxoid LPS (436; 4.2%/5-y OS:88%), PNET (205; 2.0%/5-y OS:58%), round cell LPS (183; 1.8%/5-yOS: 70%), alveolar RMS (122; 1.2%/5-yOS: 25%), malignant SFT (86; 0.8%/5-yOS: 77%), clear cell sarcoma (63; 0.6%/5-yOS: 67%), LGFMS (60; 0.6%/5-yOS: 82%), desmoplastic round cell tumor (56, 0.5%/5-y OS: 11%), ESMCS (54; 0.5%/5-yOS:78%), ASPS (48; 0.5%/5-yOS: 66%), EHE (42; 0.4%/5-yOS: 55%), and sclerosing epithelioid fibrosarcoma (28; 0.3%/5-y OS: 70%). All TRS (2,143 cases; 20.8%) are associated with younger age (40.6 versus 60.0; $p < 0.0001$), low rate of predisposing conditions (0.01% vs 22.3%, $p < 0.0001$), and higher rate of N involvement (4.7 vs 1.3%, $p < 0.0001$ and higher rate of synchronous metastasis (11.9 vs 6.7%, $p < 0.001$). R0 resection (41.6 versus 31.9%, $p < 0.0001$), use of (neo)adjuvant radiation therapy (62.6 vs 42.2%, $p < 0.0001$) and use of (neo)adjuvant CT (36.6 versus 22.3, $p < 0.0001$) were significantly more frequent. At the end, TRS are associated with a lower rate of local relapse (18.1 vs 26.0%, $p < 0.0001$) but a higher rate of metastasis relapse (42.0 vs 30.7%, $p < 0.0001$).

Conclusions: TRS display specific pattern compared to other sarcomas. Second opinion by expert pathologist and use of molecular biology confirmatory test are of major importance to recognize this population and discuss multimodal approach at early stage of the disease.

Legal entity responsible for the study: Centre Oscar Lambret, Lille, France

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1479PD Phase II study of TAS-116, an oral inhibitor of heat shock protein 90 (HSP90), in metastatic or unresectable gastrointestinal stromal tumor refractory to imatinib, sunitinib and regorafenib

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Background: Mutated KIT and PDGFRA in gastrointestinal stromal tumor (GIST) rely on HSP90 for their functional stability; therefore, HSP90 is a rational therapeutic target in treating GIST in patients (pts) acquired resistance to approved tyrosine kinase

inhibitors. TAS-116 is an oral non-ansamycin, non-purine, non-resorcinol, highly selective inhibitor of HSP90α/β with antitumor activity in an imatinib-resistant human GIST xenograft mouse model. In a phase I study, TAS-116 demonstrated the acceptable safety and the efficacy signs in radiological imaging in pts with GIST including 1 partial response. Here, we conducted a phase II study to evaluate the safety and efficacy of TAS-116 in metastatic or unresectable GIST refractory to standard therapies.

Methods: This was a phase II, open label, single-arm, multi-center study. The key eligibility criteria were histologically confirmed GIST refractory to imatinib, sunitinib, and regorafenib; a measurable lesion per RECIST ver. 1.1; and adequate organ function. Pts received 160 mg/day TAS-116 on a 5-days-on/2-days-off schedule. The primary endpoint was progression-free survival (PFS); secondary endpoints included objective response rate, disease control rate, overall survival, and adverse events. An independent central review (ICR) committee assessed all responses. Sample size was 40 for full analysis set.

Results: From 12 May 2016 to 26 April 2017, 40 pts were enrolled in this study. The numbers of prior treatments was 3 in 24 pts, 4 in 9 pts, and ≥5 in 7 pts. In 34 pts evaluated as of 26 April 2017, the most common adverse events were diarrhea (82%), anorexia (50%), increased serum creatinine (44%), and eye disorders (21%). All eye disorders recovered or resolved following dose interruption, and were limited to Grade 1. There were no treatment-related deaths. According to ICR, median PFS was 4.5 months (95% CI, 2.9–6.1 months). Although none had a partial response, 27 out of 34 pts (79%) had stable disease for ≥6 weeks.

Conclusions: TAS-116 was well tolerated and the initial efficacy results in a ≥ 4th-line treatment setting for metastatic or unresectable GIST, are encouraging. Updated data will be presented at the meeting.

Clinical trial identification: JapicCTI-163182

Legal entity responsible for the study: Taiho Pharmaceutical co., LTD.

Funding: Taiho Pharmaceutical co., LTD.

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1480PD A phase 2 study of CMB305 and atezolizumab in NY-ESO-1+ soft tissue sarcoma: Interim analysis of immunogenicity, tumor control and survival

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Background: CMB305 is an active immunotherapy designed to generate and expand anti-NY-ESO-1 immune response (IR). CMB305 consists of a dendritic cell-targeting lentiviral vector encoding NY-ESO-1 (LV305), and a boost with an NY-ESO-1 recombinant protein plus GLA-SE (G305), a TLR-4 agonist. Phase 1 studies of LV305 and CMB305 showed this approach is safe, generates IR and appears to impact survival with 81% 1-yr survival in NY-ESO-1+ sarcoma patients (pts) following LV305 treatment. We evaluated efficacy and IR for combination of CMB305 (C) and atezolizumab (A) or A alone in NY-ESO-1^{+} synovial sarcoma (SS) and myxoid round cell liposarcoma (MRCL).

Methods: A prospective randomized open label phase 2 study of C (LV305 Intradermal Days 0, 14, 42, 70 + G305 Intramuscular Days 28, 56, 84 then q6wk up to one year) + A (1200mg IV q3wk) vs. A alone in locally advanced or metastatic NY-ESO-1+ SS/MRCL. Primary endpoints are progression free survival (PFS) and overall survival (OS) with secondary endpoints of safety, IR, and response rate.

Results: As of December 30, 2016, 58 patients were enrolled. A prespecified interim analysis of PFS included the first 36 pts with median 7.0 mos follow up (Arm A+C: median age 47 yrs, 78% SS, 100% metastatic, 78% = >2 chemotherapy; Arm A: median age 44 yrs, 56% SS, 67% metastatic, 56% = >2 chemotherapy). Combination A+C was well tolerated. Clinical benefit was similar between arms (Arm A+C: 8/18 pts with SD, 1 pt unconfirmed PR, 6 mos PFS rate 17%; Arm A: 10/18 pts SD, 6 mos PFS rate 22%). In addition, anti-NY-ESO-1 IR seen in 10/19 (53%) pts Arm A+C vs. 3/12 (25%) pts Arm A by T Cell ELISpot, and 9/22 (41%) pts Arm A+C vs. 0% Arm A by antibody ELISA. Pts with IR had target lesion increase of 2% compared to 18% in pts without IR based on preliminary ANOVA-model based analysis. No deaths observed in pts with induced anti-NY-ESO-1 T cell IR (0/13 deaths IR^{+} pts vs. 5/18 deaths IR^{-} pts).

Conclusions: In the interim analysis, Arm A+C resulted in a higher level of anti-NY-ESO-1 IR when compared to Arm A; pts with IR tend to have better target lesion control. Early data indicate that induction of anti-NY-ESO-1 IR may be associated with better survival.

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Legal entity responsible for the study: Immune Design

Funding: Immune Design

Disclosure: S. Chawla: Board of Directors/Stock: Prana, Uptick Health, Counterpoint Biomedical. Honoraria: Amgen, Threshold, Cytrx, Pharmamar, J&J, Tracon, Morphetek. Research project: Amgen, Threshold, Cytrx, Pharmamar, J&J, Tracon, Morphotek, BMS, Etsai, Immune Design. B.A. Van Tine: Stock ownership: none Membership on Advisory Board Novartis Lilly Janseen Epizyme Karyopharm Diiachi Board of Directors none Corporate sponsored research Pfizer Merck Speakers Beuro Caris Janseen Lilly. K. Ganjoo: Compensation to author for Advisory board with both Daiichi Sanko and Novartis. R.F. Riedel: Sponsored Research/Advisory Board: AADi, Arog, Daiichi-Sankyo, Karyopharm, Lilly, Novartis, Oncternal, Plexxikon, SARC, Threshold, Tracon, Tokalas. Eisai, EMD-Serono, Ignyta, Immune Design, Janssen. Consultant: Lilly, The Oncology Consortium. S. Attia: Compensation (to Mayo Clinic) as Principal Investigator from: AB Science, Morphotek, Threshold Pharmaceuticals, Tracon Pharma, ZioPharm, CytRX, Bayer, Novartis, Daichii, Bayer, Lilly, Immune Design, Karyopharm Therapeutics, Epizyme. E. Choy: Consulting fees from Amgen, EMD Serono, Daiichi, Bayer. M. Agulnik: Advisory board: Novartis, Janssen, Eisai and Lilly. V. Keedy: Consultant Karyopharm Janssen Research funding to institution for sponsored research: Lilly, Plexxicon, CytRx, Daiichi, Threshold, Janssen, Roche, Astrazeneca, MedPacto, Immune Design, GSK. T. Philip: Consultant: Novartis. C. Bohac: Employed by Immune Design. Stock ownership with Amgen, Immune Design H. Lu: Employee of Immune Design and Stock ownership Immune Design. M. Chen: Employee of Immune Design and Stock Ownership Immune Design. R. Maki: Clinical Trial support (institution), consulting fees, travel: Immune Design. All other authors have declared no conflicts of interest.

1481PD Efficacy and safety of palbociclib in patients with advanced gastrointestinal stromal tumors refractory to imatinib and sunitinib

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Background: p16/CDKN2A loss play a crucial role in GIST progression. Therapeutic options after *progression* to *imatinib* and *sunitinib* are limited. Palbociclib, an oral small-molecule inhibitor of cyclin-dependent kinases 4 and 6, was recently approved for postmenopausal women with advanced hormone receptor–positive, her2-negative breast cancer. Preclinical studies show that palbociclib inhibits the cell cycle and growth in cells with decreased p16.

Methods: This is a multicenter single-arm phase 2 clinical trial based on 2-stage Simon's design which assesses safety and efficacy of palbociclib in patients (pts) with advanced GIST having failed at least on imatinib and sunitinib and with CDKN2A loss assessed by CGH array. All pts had to have documented progressive disease (PD) as per RECIST 1.1 before study entry. Pts receive palbocilcib 150mg day 1-day 21 (oral route), daily until PD or unacceptable toxicity. The primary endpoint is the 4-month non-PD rate according to RECIST 1.1. Based on the following hypotheses: 25% 4-month non-PD rate (H0), 45% acceptable 4-month non-PD rate (H1), 5% type I error rate, 90% power, a total of 57 assessable pts are necessary (22 for the first stage + 25 for the second stage). Following the inclusion of the first 22 pts, if ≥ 7 pts are progression-free at 4 months, the accrual will continue. In order to account for not assessable pts (+/- 10%), 63 pts will be of the French Sarcoma Group.

Results: As of May 2017, 72 pts (52 males, 20 females) have been included in the study. Median age is 66.0 years out of the first 22 first evaluable patients had progressive

disease at 4 months indicating that palbociclib had not reached the primary endpoint to justify continuing accrual after the 1st step of the study.

Conclusions: Palbociclib has no significant activity as a single agent in advanced GIST with p16/CDKN2A loss. Prognostic value of CDKN2A loss in the whole population will be presented at the meeting.

Clinical trial identification: NCT01907607

Legal entity responsible for the study: Institut Bergonié

Funding: INCA

Disclosure: All authors have declared no conflicts of interest.

1482PD Notch pathway inhibition with LY3039478 in soft tissue sarcoma (STS) and gastrointestinal stromal tumours (GIST)

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Background: LY3039478 (LY) is an orally bioavailable selective Notch inhibitor (Notch 1-4). Here we report on safety, pharmacodynamics (PD), and anti-tumour activity of LY in patients (pts) with STS/GIST.

Methods: This ongoing, multi-part, phase 1 trial enrolled pts with refractory advanced or metastatic STS and GIST, measurable disease, ECOG score $\leq$1, and baseline tumour tissue. Eligible pts received LY 50 mg three times per week (TIW), for a 28-day cycle until disease progression. Safety assessments were based on CTCAE V4.0. Tumour responses were assessed using RECIST 1.1 and Choi criteria. Primary objectives are to confirm the recommended phase 2 dose of LY and document antitumour activity. Secondary objectives are safety and toxicity, PD, progression-free survival (PFS) and overall survival (OS).

Results: 63 pts have been enrolled and received LY (24 males, 39 females; median age 58, range 31-76). 26 pts had leiomyosarcoma (LMS), 9 liposarcoma, 7 pleomorphic sarcoma, 6 angiosarcomas, 5 rhabdomyosarcoma and 10 GIST. 18 out of 39 (46%) pts with evaluable tumour samples were positive for Notch 1 ICD. 5% and 13% were positive for Notch 2 ICD, and Notch 3 respectively. Per RECIST, 2 out of 53 pts with STS had unconfirmed PR, and 20 SD. In GIST group, 4 pts had SD. Using Choi Criteria, 5 pts in STS had unconfirmed PR. Overall median PFS was 1.74 months (95% CI: 1.68-2.60) and consistent across histology groups (median PFS=2.23, 1.91 and 1.68 months for LMS, GIST and other STS, respectively). PFS rate at 3 months was 42% in LMS, 39% in GIST and 15% in other STS respectively. OS and biomarker/histologic analyses of pre and post treatment biopsies will be presented at the meeting. Most frequent related adverse events (all grades) occurring in $\geq$ 20% of pts included diarrhoea 44 (70%), vomiting 24 (38%), nausea 21 (33%), decreased appetite 17 (27%), fatigue 17 (27%) asthenia 16 (25%), hypophosphataemia 14 (22%).

Conclusions: LY suggested activity in pts with STS and GIST and had a manageable safety profile.

Clinical trial identification: Trial protocol number: Protocol I6F-MC-JJCA(e) Clinicaltrials.gov ID: NCT01695005 Release date: 08-July-2016

Legal entity responsible for the study: Eli Lilly and Company

Funding: Eli Lilly and Company

Disclosure: O. Mir: Speaker Bureau: Eli Lilly, Roche. Consulting/advisory board member: Amgen, Astra-Zeneca, Bayer, BMS, Eli Lilly, Netcancer, Novartis, Pfizer, Roche, Servier. A. Azaro: Member of Orion SMB. J.R. Merchan: Consulting/Advisory role: Exelixis. Research Funding: Rexahn, Eli Lilly, Novartis, Tocagen, Agensys, Tracon. R. Chugh: Stakeholder: Portala. Advisory board member: EMD Serano, Epizyme. Research funding: Eli Lilly, Novartis, Morphotek, Mabvax, Epizyme. J.C. Trent: Member of advisory board: Eli Lilly, Janssen, Eisai, Novartis, Eayer, Blueprint, Deciphera. J. Rodon: Advisor/board member: Eli Lilly, Novartis, and Servier. U. Ohnmacht: Stakeholder: Eli Lilly and Company. A. Le Cesne: Received honoraria: PharmaMar, Lilly, Amgen, Novartis, and Pfizer. J-C. Soria: Advisory board member: Eli Lilly and Company. C. Massard: Advisory board member, speaker, investigator: Amgen, Astellas, Astra Zeneca, Bayer, Celgene, Genentech, Ipsen, Janssen, Eli Lilly, Novartis, Pfizer, Roche, Sanofi, Orion. All other authors have declared no conflicts of interest.

1483PD Imatinib in combination with everolimus in patients with progressive advanced chordoma: results form an Italian phase 2 clinical trial

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Background: To evaluate the antitumor activity of imatinib in combination with everolimus in patients (pts) with advanced PDGFB- and/or PDGFRB-positive chordomas with evidence of mTOR and/or of its effectors (i.e. S6, 4EBP1) activation.

Methods: Within an Italian academic prospective phase II clinical study carried out from January 2011 to March 2015, 45 patients with advanced PDGFB/PDGFRB and mTOR/S6/4EBP1 positive chordoma received imatinib 400 mg/day in combination with everolimus at the starting dose of 2.5 mg/day, until progression or limiting toxicity. Eligible pts had to have evidence of progression in the 6 months prior to study entry. The primary endpoint was overall tumor response rate (ORR), defined by the Choi criteria applied also to MRI. Secondary endpoints were RECIST response, progression-free survival (PFS), overall survival (OS).

Results: Fifteen of 45 pts included in the study were pretreated with imatinib (as a single agent). All pts completed their treatment (22 progression; 16 toxicity; 7 other). Among 38/46 patients evaluable by Choi criteria, the best response was: 8 partial response (PR) (ORR, 21%), 23 stable disease (60%) and 7 progression. 42/46 pts were evaluable by RECIST with 1 PR (2%), 36 SD (85%) and 3. Median PFS by Choi criteria was 10 months (range 1-45), with 36% and 17% pts disease-free at 12 and 24 mos, respectively. Median PFS by RECIST was 13 months. At a median follow-up of 31 months, median OS was 47 months.

Conclusions: Although formally negative (the planned target was a Choi ORR $\geq$60%), this study showed that imatinib + everolimus is active in a proportion of progressive advanced chordoma pts. Major dimensional responses were uncommon but disease stabilization was apparently longer than observed with imatinib as a single agent. Toxicity was not negligible.

Clinical trial identification: EudraCT number: 2010-021755-34

Legal entity responsible for the study: Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

Funding: AIFA (Agenzia Italiana per il Farmaco)

Disclosure: S. Stacchiotti, E. Palassini, A.M. Frezza: Novartis, research funding to my Institution for clinical trial in which I am involved. A. Gronchi: Novartis: Advisory Board (compensated), Honoraria. P.G. Casali: Novartis, Advisory Board (compensated), Honoraria, Research funding to my Institution for clinical trial in which I am involved. All other authors have declared no conflicts of interest.

1484PD A matching-adjusted indirect comparison of trabectedin and pazopanib for the treatment of advanced, metastatic, leiomyosarcomas

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Background: Trabectedin (T) and pazopanib (P) are approved treatments for locally advanced or metastatic leiomyosarcoma (L-mSTS). In the absence of head-to-head randomized controlled trials (RCTs); a matched indirect comparison (MAIC) was performed to assess potential differences in clinical efficacy between the treatment groups.

Methods: MAIC was performed by extracting baseline characteristics from two phase III RCTs: SAR 3007 (T) and PALETTE (P): individual patient level data (IPD) was available forT only aggregated was published for P. Excluding those T patients who did not meet inclusion criteria for PALETTE, a sample size of 372 L-mSTS patients (T = 263, P = 109) was generated. Of all baseline characteristics, only time since diagnosis ($\geq$30 vs. < 30 months), age ($\geq$65 vs. < 65 years), and body weight ($\geq$77 vs. < 77 kilograms), were statistically significant outcome predictors with T. The generalized method of moments (GMM) was used to optimally match cohorts for evaluation of

differences in overall survival (OS), progression-free survival (PFS), and safety. Statistical analysis was performed using "R".

Results: There was no statistically significant difference in PFS [HR = 0.82, (95%CI 0.63-1.06, p = 0.13)], or OS [HR = 0.86, (95% CI 0.64-1.18, p = 0.36)]. The percentage of patients with post-progression therapies was higher in T (74.5%) vs. P (59%) group. In the subgroup with PFS ≥6 months, patients treated with T experienced significantly improved median PFS (11.2 months vs PFS 8.4 months HR: 0.47 (95% CI: 0.3007 – 0.7434), p = 0.002 and were significantly more likely to achieve long term survival (OS ≥ 18 months): 45.8% vs. 33.7% (95%CI: 23.5%-48.3%), p = 0.025. Increased myelosuppression and hepatotoxicity observed with T whereas diarrhea, hypertension, pulmonary toxicity/pneumothorax, and neurotoxicity were observed with P.

Conclusions: The MAIC model warrants further investigation and validation. No differences in mPFS or mOS were noted in a MAIC comparison. Among patients achieving long term disease control (PFS > 6 mo), T significantly increased mPFS and the proportion of patients achieving prolonged overall survival (OS ≥ 18 mo). Differences in the safety profile were highlighted by this indirect comparison.

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1485P Localized undifferentiated endometrial sarcomas (LUES): Results of a French Sarcoma Group (FSG) retrospective series of 39 patients (pts)

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Background: UES are tumors of very bad prognosis. Although large surgical resection is the cornerstone of curative intent treatment, the optimal post-operative strategy remains unclear.

Methods: We conducted a retrospective analysis of LUES pts (Stade I-III) over the last 8 years in 10 FSG centers, from Netsarc and RRePs databases.

Results: Thirty-nine pts with primary LUES treated from 2008 to 2016 were included, with median age of 61 years (range, 43-80), and median ECOG of 0 (range, 0-3). Metrorrhagia, abdominal pain, and pelvic mass bleeding were the most common symptoms. The locoregional extension report usually included: gynecological examination (71%), and/or pelvic MRI (83%) and/or abdomino-pelvic CT scan (43%). The remote extension report was performed preoperatively for only 17/39 (50%) pts. Among 39 LUES, 24 (67%) were stage I, 3 (8%) stage II and 9 (25%) stage III. All the patients were operated on and surgical procedures were radical hysterectomy and bilateral oophorectomy for 26/39 (70%).Tumor resections were mostly R0, 23/39 (74%) and R1, 6/39 (19%). Tumor rupture occurred in 6 pts. For 7/39 LUES there was a positivity of hormonal receptors and/or cyclin D1. Twenty-two (56%) received post-operative radiotherapy (11 of them with complementary brachytherapy) and 11 (31%) adjuvant chemotherapy. With a median follow-up of 33 months (0.3-112), 17/39 pts are alive, 21/39 (54%) relapsed (7 local relapse and 13 metastases). The 3- and 5-year Overall Survival (OS) rates are 49.8% and 31.1% respectively. Median OS and Relapse-Free Survival (RFS) are 32.7 (16.3-49.1) and 23 (4.4-41.6) months, respectively. In univariate analysis; early FIGO stage (p < 0.0001), complete resection (R0-R1 vs R2; p = 0.027), ECOG (p = 0.02) and adjuvant radiotherapy (p < 0.0001) were associated with a better OS; vascular invasion (p = 0.024) and adjuvant radiotherapy (p = 0.021) were associated with a better RFS.

Conclusions: Treatment of primary LUES is radical hysterectomy and bilateral oophorectomy. Adjuvant radiotherapy appears beneficial for RFS and OS. The FIGO stage seems to have an impact on OS. A prospective study could be carried out to validate this therapeutic management.

Legal entity responsible for the study: invalid

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1486P An epidemiological insight into epithelioid sarcoma (ES): The open issue of distal-type (DES) versus proximal-type (PES)

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Background: ES is a rare sarcoma with distinctive pathologic and clinical features as well as the potential to respond to new targeted agents. We used the RARECAREnet and the SEER18 cancer registry (CR) databases (DB) to highlight the epidemiological hallamrks of ES in the EU and in the US.

Methods: The ICD-O3 code 8804 applies both to the DES and PES. Thus we broke down the primary sites using the ICD-O3 topography codes, to separate the anatomically proximal and distal forms, as a partial surrogate for the two entities of DES and PES. Incidence rate (IR), world-age adjusted IR and relative survival (RS) were calculated for ES patients diagnosed in the period 2000-07 and followed-up at least up to 31st Dec 2008. RS was estimated by the Ederer II method. 497 new cases of ES were identified from available registries in the EU, 301 in the US.

Results: Crude IR was 0.03/100,000 in the EU and 0.05/100,000 in the US. Age-adjusted IR were 0.02/100,000 and 0.05/100,000 respectively. M:F ratio was 1.6 in both sets of registries. Mean age at diagnosis was 46 in the EU and 44 yrs in the US. IR increased with age (higher in > 75-yr patients). IR in the childhood population (<14 yrs) was 0.01, i.e., 5% of all new ES cases. IR was similar for anatomically distal and proximal groups, but the latter was more incident in older patients. 5-yr RS was 50% and 52% in the EU and US, respectively. In both registries, 5-yr RS was higher in anatomically distal than in anatomically proximal (EU: 65% vs 38%; US: 69% vs 34%), evenly across all age groups (Table).

Conclusions: ES is a very rare cancer, exceedingly low in childhood. Prognosis is serious, making the identification of new treatments a priority. New targeted agents are currently under study. However, the distinction between DES and PES is likely to be of major prognostic significance. In fact, using anatomical location as a proxy, though inappropriate, we could see clear-cut differences in the epidemiological outcome. An effort to stratify ES patients by their pathologic subtype is warranted in all studies, all the more on new agents.

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Table: 1486P Incidence and 5-years overall survival rates according to patient age and primary tumour site. * NE= not estimable for limited number of cases. DES: distal-type epithelioid sarcoma; PES: proximal-type epithelioid sarcoma.

Age (yrs)	Incidence (/100.000)	5-yrs OS (95% CI)	DES 5-yrs OS (95% CI)	PES 5-yrs OS (95% CI)
0 - 14	**EU:** 0.01 **US:** 0.01	**EU:** 53% (27-74) **US:** 90% (47-99)	**EU:** 67% (27-88) **US:** 89% (42-98)	**EU:** NE* **US:** NE*
15 - 39	**EU:** 0.02 **US:** 0.05	**EU:** 68% (59-75) **US:** 66% (56-74)	**EU:** 79% (68-86) **US:** 71% (60-80)	**EU:** 51% (37-63) **US:** 54% (36-69)
> 40	**EU:** 0.03 **US:** 0.06	**EU:** 39% (32-46) **US:** 39% (30-47)	**EU:** 49% (37-61) **US:** 62% (45-75)	**EU:** 33% (25-41) **US:** 26% (17-35)

1487P Natural history of alveolar soft part sarcoma (ASPS): Impact of brain metastases and role of anti-angiogenic therapies (AAT)

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Background: ASPS is a rare sarcoma subtype with clinical specificities, such as an indolent behavior, brain metastasis and resistance to doxorubicin. AAT have shown clinical activity in this setting, but little is known on the optimal therapeutic strategy, and the management of brain metastasis (BM).

Methods: We retrospectively analyzed patients (pts) treated in 3 referral centers of the French Sarcoma Group. Factors associated with BM development and overall survival (OS) were analyzed. In addition, progression-free survivals (PFS) under AAT in patients with and without BM were reported.

Results: We identified 75 pts [median age at diagnosis: 23 (5-96 years), 61% females]. Among those, 31 (41%) pts had documented synchronous lung metastasis (LM), and none had BM. Median OS in pts with localized and metastatic disease were 279 months, (95% CI, 279-NR) and 74 months (95% CI, 62-144) (Log-rank, $p = 0.002$), respectively. Only surgical complete resection (R0) was associated with better OS in localized disease (HR = 4.3; (95% CI, 1-19.3), $p = 0.056$). Fifty-two (69%) pts had documented LM in the course of the disease; among those, 13 (17%) pts developed BM within a median interval of 35 months (95% CI, 17-48) from LM. Initial tumor size was associated with BM-free-survival ($\geq$5cm *vs* <5 cm): HR = 6.7 (95% CI, 1.7-26). Twelve pts were treated with AAT (sunitinib, n = 10) including 5 (42%) with documented BM; median PFS under AAT were 2 months (95% CI, 1.3-2.7) for pts with BM and 11 months (95% CI, 9-18) for pts without BM, respectively (p=0.004). BM was the cause of death or major contributing factor to it in 36% of pts.

Conclusions: These data highlight the indolent course of the disease leading to BM, which turned a shift in the course of the disease, along with limited efficacy of AAT in this setting. Furthermore, they suggest that the appropriate timing for AAT introduction has to be discussed in an individual basis considering the PFS/OS ratio in pts with metastatic disease.

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1488P Treatment patterns, clinical outcomes and prognostic factors of visceral angiosarcoma (V-AS): A report from the Asian Sarcoma Consortium (ASC)

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Background: We previously reported on the real world treatment and outcomes of 423 angiosarcoma pts in Asia. In this current report, we focus on the 173 pts with V-AS and evaluate the treatment patterns and prognostic factors associated with this disease subset.

Methods: This is a retrospective chart review of V-AS pts seen at 8 Asian academic study sites. Survival analysis is measured from date of presentation to the study site.

Results: Median study follow-up was 8.7 mths. Median age 52 yrs; 86% of pts presented with primary disease to study site. 42% (n = 73) had localized disease and 56% (n = 97) had locally advanced/unresectable or metastatic disease; disease status was unknown for 3 pts. Distribution of primary site as follows, liver (n = 38, 22%), cardiovascular system (n = 30, 17%), breast (n = 25, 14%), spleen (n = 18, 10%) and others (n = 62, 36%) from a myriad of organ systems each representing <10% of cases. More pts with breast AS presented with localized disease. For pts with localized disease, primary treatment was surgery in 74% (n = 54) of pts. Of 38 pts with known margins, R0 and R1 were achieved in 71% and 21% respectively. In pts who had surgery, 43% developed subsequent disease relapse/progression with a median PFS of 9.5 mths. Of 97 pts with advanced/unresectable disease, 59% of pts received chemotherapy as part of treatment while 22% and 20% had surgery/radiation only or supportive care only respectively. 46% of chemotherapy-treated pts had 1 line of treatment while 35% and 19% had 2 or > 3 lines of treatment respectively. The most common first line chemotherapy used was paclitaxel (53%) followed by liposomal doxorubicin (18%). Median OS was 11.9 mths in the overall V-AS cohort, with median OS 29.2 mths and 6.3 mths in the localized and advanced/unresectable cohort respectively. In the univariate analysis of pts with unresectable/metastatic disease, only ECOG was associated with OS.

Conclusions: This study highlights the heterogeneity and treatment challenges of visceral angiosarcoma. Overall prognosis is poor, in particular in pts with advanced/unresectable disease.

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1489P High dose loco-regional chemotherapy for locally advanced angiosarcoma: A multicenter study

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Background: Angiosarcomas are rare aggressive sarcomas that count for 2% of all soft tissue sarcomas. The only potential curative treatment is complete surgical excision, but a large subset of patients present with locally advanced disease. The aim of this study was to evaluate the effectiveness of Isolated Limb Perfusion (ILP) as an alternative treatment option for locally advanced angiosarcoma in the extremities.

Methods: All patients who underwent an ILP for angiosarcomas between October 1991 and October 2016 in three tertiary referral centres were identified from 3 prospectively maintained databases. Demographics, tumour, treatment and response characteristics and the disease course were all obtained from either the database or patient files. Statistical analysis was performed using SPSS statistics 24.

Results: A total of 39 patients were included. The median age was 66 (range, 24-95) years. Of these patients, 23 (59%) patients had a complete resonse after ILP, 10 (25.6%) patients had a partial response, 4 (10.3%) had stable disease and 2 (5.1%) patients had local progression immediately after ILP. Of all patients, a total of 22 patients developed local progression (56,4%) while 10 (25.6%) developed distant metastases. Median time to progression; 7,4 months (IQR 3-14,9) and median time to distant metastasis of 6,4 months (IQR 1,5-44,9). The 10 (25,6%) patients with a complete response (compared to PR/SD/PD) had a non-significant trend towards better median overall survival (81,2 vs 14,5 months) (p = 0,054), and had a significantly prolonged median progression free survival (15,4 vs. 7,3 months) (p = 0,015). A total of 5 patients underwent multiple ILP's whereby the complete response rate of the first, second and third ILP were 60% (n = 4/6), 80% (n = 4/5) and 67% (n = 2/3) respectively. Only 13 (33,3%) patients needed further surgical intervention, consisting of wide local excision in 8 patients (20,5%) and amputation in 5 patients (12,8%).

Conclusions: ILP should be considered as treatment option in the multidisciplinary management of patients with locally advanced limb angiosarcomas, resulting in a high limb salvage rate, high number of complete responses and prolonged progression-free survival.

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Disclosure: All authors have declared no conflicts of interest.

1490P Primary cardiac sarcoma (PCS): A multi-national retrospective review of clinical experience

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Background: Primary cardiac sarcoma (PCS) is a rare but often fatal disease. The current study aimed to analyze the impact of baseline demographics, local and systemic therapies in a contemporary cohort.

Methods: Clinical records of PCS across five institutions in three continents were reviewed and collected. Kaplan-Meier method was used to estimate survival. Cox proportional hazard model was used to associate variables to progression-free survival (PFS) or overall survival (OS).

Results: 47 pts with PCS (1996-2016) with a median follow-up time of 12.9 months (ms) were identified. The median age at diagnosis was 41 (range 18-79); 43% (n = 20) presented with metastatic disease. Tumor equally originated from right- (n = 23) and left-sided heart (n = 23). The common histologies were angiosarcoma (n = 18, 38%), intimal sarcoma (n = 8, 17%), and sarcoma NOS (n = 10, 21%). 66% (n = 31) had surgical (S) treatment for PCS, and only 4 (13%) pts had R0 resection. The median primary lesion size was 49 mm (20-84 mm). 70% (n = 33) of pts received at least one line of chemotherapy (C), and 51% (n = 24) received multi-modality treatment (45% S + C, 4% S + XRT, 2% S + C + XRT). The median OS was 17.7 ms (95% CI 12.4-21.8 ms). For all pts, age $\geq$ 65 was the only significant negative prognostic factor (HR 7.43, $p < 0.01$, Table 1). In localized PCS, angiosarcoma histology was a significant factor for worse PFS (HR 3.05, $p = 0.04$) and OS (HR 2.56, $p = 0.11$). 29 metastatic or relapsed pts received C. For first-line palliative C (52% combination, 48% single agent), the median PFS was 3.8 ms (95% CI 1.5-6.9 ms). The best response for first-line C was PR 10 (35%), SD 4 (14%), PD 12 (41%). 60% (6/10) of pts with PR were treated with anthracycline (angiosarcoma n = 5; intimal sarcoma n = 1). No significant improvement in OS was identified in pts presenting throughout the 20 year period of this review (pre- vs post 2012; HR 1.1, $p = 0.81$).

Table: 1490P Prognostic factors for all pts

Variable	HR (95% CI)	P Value
Age $\geq$ 65	7.43 (2.54-21.72)	0.0002
Metastatic disease at diagnosis	1.87 (0.90-3.88)	0.09
Multi-modality treatment	0.64 (0.32-1.27)	0.20
Angiosarcoma histology	1.58 (0.72-3.47)	0.26

Conclusions: The prognosis of PCS remains poor without significant improvement in OS compared to historical levels. Further research is required for this rare entity.

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Disclosure: All authors have declared no conflicts of interest.

1491P Primary cardiac sarcoma: A retrospective study in two Korean tertiary centers

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Background: Primary cardiac sarcoma(PCP) is a rare diasease with dismal prognosis. Optimal treatment strategy for PCP is not clear.

Methods: We retrospectively reviewed patients diagnosed with PCS in two institutions in Korea, between 1996 and 2013. A total of 41 patients were identified. Clinical characteristics and treatment outcomes were investigated. Survival was estimated and compared by Kaplan-Meier method and Log-rank test.

Results: Median age was 44 years. Eighteen patients (43.9%) were male. The most common type was angiosarcoma (N = 20, 48.7%), followed by poorly-differentiated sarcoma (N = 7, 17.1%). Most tumors were located in atriums (N = 27, 65.9%). At diagnosis, 31 patients (75.6%) had localized disease. Surgical resection of primary cardiac tumor was performed in 28 cases (68.3%) and microscopic complete resection were achieved in 12 localized cases. Median overall survial was 13.2 months for entire patients, 17.0 months after complete resection, 17.9 months after incomplete resection and 5.7 months in non-resected cases. Patients who received adjuvant chemotherapy and/or radiotherapy after surgery had significantly better median OS of 21.6 months than 11.0 months of those received surgical resection alone without adjuvant treatment ($p = 0.007$).

Conclusions: Surgical resection and multidisciplinary treatment were associated with better survival in patients with primary cardiac sarcomas. Aggressive multidisciplinary approaches may have a role in subset of patients with primary cardiac sarcomas.

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Disclosure: All authors have declared no conflicts of interest.

1492P The differences in recurrence and survival of extremity liposarcoma subtypes

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Background: Liposarcomas (LPS) are most frequently located in the extremity and recur often, locally as well as on distant sites. There are currently no studies comparing the differences between the different LPS subtypes specifically on this primary site. The aim of this study is to map the differences in recurrence and survival of extremity LPS.

Methods: Two retrospective databases (Rotterdam-R, Warsaw-W) of patients treated for primary LPS located in the extremities from 1985-2015 in two tertiary referral centers were used to analyze recurrence patterns (local/distant) and survival.

Results: In total, 456 patients were identified: 192 with well differentiated LPS (WDLPS), 172 myxoid LPS (MLPS), 54 pleomorphic LPS (PLPS), 23 dedifferentiated LPS(DDLPS) and 15 other subtypes (excluded from further analysis). A difference between the two datasets was the frequency of (neo)adjuvant radiotherapy (R: 34.9% vs. W: 81.5%). In the Rotterdam cohort, local recurrence (LR) was observed most frequent in DDLPS (4/13, 5-year LR free survival 56.6%), followed by WDLPS (26/113, 64.9%), PLPS (3/20, 78.6%) and MLPS (10/77, 84.0%, $p = 0.136$). In the Warsaw cohort, 5-year LR free survival was the lowest in PLPS (9/34, 67.7%), followed by DDLPS (1/10, 83.3%), MLPS (12/95, 84.9%) and WDLPS (3/79, 94.1%, $p = 0.001$). Distant metastases (DM) were most commonly observed in PLPS in both datasets (5-year DM free survival R: 9/20, 50.3% and W: 16/34, 44.5%), but in the Rotterdam cohort MLPS (16/77, 76.3%) was the second most common subtype with DM, compared to DDLPS (2/10, 62.5%) in Warsaw. DM in WDLPS was rare in both datasets (R:3/113, 96.3%, W: 1/79, 98.5%). 5-year overall survival (OS) did not significantly differ between the two datasets (R: 38/223, 78.5% vs. W: 32/218, 80.9%, $p = 0.561$), but did significantly differ between the subtypes (R: $p = 0.005$, W: $p < 0.001$). In both datasets, 5-year overall survival was poorest in PLPS (R: 8/20, 57.5%, W: 15/34, 38.8%) and DDLPS (R: 4/13, 59.9%, W: 3/10, 44.4%), followed by MLPS (R: 16/77, 75.6%, W: 13/95, 83.1%) and WDLPS (R: 10/113, 88.2%, W: 1/79, 98.5%).

Conclusions: Patients with the four LPS subtypes show distinct patterns of LR, DM and OS. Despite the differences in recurrence, treatment and follow up, OS did not differ significantly between the two expertise centers.

Legal entity responsible for the study: Erasmuc MC Rotterdam

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1493P The sarcoma policy checklist: Focusing policy efforts on sarcoma

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Background: The Sarcoma Policy Checklist was developed by a multi-stakeholder group of experts to help policymakers prioritise actions to close the gap in access to high-quality information and care for sarcoma patients in Europe.

Methods: Experts defined five key areas where policy efforts are most needed to improve the care of sarcoma patients across Europe. A pragmatic review of the published literature was then conducted to determine to what extent recommendations were implemented in practice. Research focused on six countries (France, Germany, Italy, Spain, Sweden and the United Kingdom) and was complemented by local expert interviews.

Results: Five key priority areas were identified by experts: Each country should have designated, accredited centres of reference for sarcoma; specialised professional training should be provided to all health care professionals involved in sarcoma care; a multidisciplinary approach to care should be offered to every patient; greater incentives for research and innovation, and more rapid access to effective treatments are needed. Most countries have specialist sarcoma centres, however, there is often a lack of defined criteria to designate specialist centres and evaluate the quality of care. Professional training is a gap in all countries, as training on rare cancers is most often not included in the general medical curriculum or in oncologists' training. More basic research is needed to understand the underlying epidemiology of sarcomas, and help focus research on effective treatments. Greater alignment between regulatory frameworks and access frameworks such as Health Technology Assessment is needed, particularly in terms of evidentiary requirements for new treatments.

Conclusions: The heterogeneity of sarcomas poses particular challenges to research, professional training and patient access to quality treatment and care. The creation of the European Reference Network (ERN) on sarcoma, and recent advances in defining essential requirements and patient-driven principles for sarcoma care will help improve the situation of sarcoma patients across Europe. This policy paper hopes to contribute to those efforts and help drive meaningful policy change to improve patient care.

Legal entity responsible for the study: The Health Policy Partnership Ltd

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1494P Dermatofibrosarcoma protuberans might not benefit from postoperative radiotherapy after local resection with negative margin

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Background: To evaluate the role of postoperative radiotherapy (RT) in the treatment of dermatofibrosarcoma protuberans (DFSP) after local resection with negative margin.

Methods: We retrospectively analyzed 84 consecutively treated DFSP patients who received local resection ($\leq$2cm) with negative margin from 2000 to 2016 in our institution. Statistical analysis was performed with a commercially available statistical software package.

Results: The median follow-up was 60 months (range, 10-201). For patients (28/84) with postoperative RT, four (4/28) patients were found to had local relapse, while three of them had $\leq$ 1 cm surgical margin. For patients without postoperative RT, four (4/56) patients had local failure. Postoperative RT failed to improve the local recurrence-free survival (LRFS) of DFSP after local resection with negative margin (Fisher=0.431). Patients with fibrosarcomatous DFSP (FS-DFSP) were found to have higher local recurrent rate than DFSP (66.7% vs. 7.4%, Fisher=0.023). Twenty-six patients were examined for ki-67, and positive range is 1-30%. Patients with high ki-67 expression (>15%) were found to have higher local recurrence rate than the others (80.0%vs0%, Fisher=0.000).

Conclusions: Postoperative RT did not improve the LRFS of DFSP after local resection with negative margin. FS-DFSP was more likely to have a local relapse than the other types. Ki-67 might become a good predictor for local control of DFSP.

Legal entity responsible for the study: Kai xin Kaixin Du

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1495P Low-dose chemotherapy with methotrexate and vinblastine for desmoid tumors: A single institution experience

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Background: Desmoid tumor (DT) is a rare and locally invasive proliferative disease. Although, the absence of metastatic potential, it has the propensity for locally invasive growth and recur. Chemotherapy may be considered in inoperable and/or recurrent disease.

Methods: Patients with histological diagnosis of DT and treated with weekly low-dose chemotherapy with vinblastine and methotrexate between January 1998 and December 2015 were identified and their medical records were analyzed.

Results: Of 23 patients analyzed, most of them were women (female-to-male ratio 2.8:1). The median age at presentation was 29 years (range, 18-59 years). Tumors location was: thoracoabdominal wall (n: 11, 47.8%), extremities (n: 7, 30.4%), abdominal cavity (n: 1; 4%), and head and neck (n: 4, 17.3%). Tumor sizes were documented in 18 cases and ranged from 3 to 20 cm in largest linear dimension (median, 10 cm). Eight (34.7%) female had pregnancy history and 2 (8%) had familial adenomatous polyposis history. Eleven (47,8%) underwent surgery as first-line treatment. Five (21.7%) patients received first-line treatment with vinblastine and methotrexate, four (17.3%) patients as second-line, and 14 (60.8%) patients as third and fourth-line. Fourteen (60.8%) patients had stable disease, four (17.3%) had partial response, and five (21.7%) patients had progressive disease during chemotherapy treatment. After a median follow-up of 58 months, 12 patients had progression disease and 2 patients died. The median PFS was 29 months, without any progression after 32 months.

Conclusions: Discussion: Weekly low-dose chemotherapy with vinblastine and methotrexate appears to have significant activity. Chemotherapy could be an acceptable alternative to radical surgery in selected patients with desmoid tumors.

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1496P EORTC experience with advanced/metastatic epithelioid sarcoma patients treated in prospective trials: Clinical profile and response to systemic therapy

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Background: Epithelioid sarcoma (ES) is a soft-tissue sarcoma (STS) associated with a high local recurrence rate after primary resection and high incidence of distant metastasis. Little is known about clinical course and response to systemic treatments. This retrospective analysis aims to provide a reference for future ES-specific studies.

Methods: Data from patients with locally advanced/metastatic ES entered in prospective multi-sarcoma phase II/III trials were pooled: EORTC trial 62012 (doxorubicin vs. doxorubicin/ifosfamide), 62043 (pazopanib), 62072 (pazopanib vs. placebo) and 62091 (doxorubicin vs. trabectedin). Patients had either a local or centrally confirmed diagnosis of ES, inoperable/metastatic disease at study entry and were eligible for the respective trial. Response was assessed using RECIST 1.1. Progression-free survival (PFS) and overall survival (OS) were calculated from date of study entry.

Results: Among 1099 patients with advanced STS, 27 ES patients (2.5%) were eligible (17 male (63%), median age at diagnosis 50 yrs, range 19-72). 18 (66.7%) received chemotherapy as 1st line treatment (5 doxorubicin, 8 doxorubicin/ifosfamide, 2 pazopanib, 3 trabectedin) and 9 (33.3%) received pazopanib in 2nd line or later. Primary tumor was located in lower extremity (N = 8; 29.6%), upper extremity (N = 5; 18.5%), retro/intra-abdominal (N = 4; 14.8%), other locations (N = 10; 37.0%). At study entry, metastases were mainly found in lung (N = 17; 63%), lymph nodes (N = 9; 33.3%), bone (N = 8; 29.6%) and soft tissue (N = 7; 25.9%). Best response for 1st line patients was 4 partial responses (PR, 22.2%), 10 stable disease (SD, 55.6%) and 4 progressive disease (PD, 22.2%). In subsequent lines, pazopanib achieved 1 PR (11.1%), 4 SD (44.4%) and 4 PD (44.4%). All patients but one progressed. Median PFS and OS were 3.8 (95% CI: 2.2-4.8) and 10.8 months (95% CI: 8.1-21.3), respectively. 5 patients were still alive at time of the according trial analysis.

Conclusions: With all limitations of a retrospective analysis of such small dataset, objective response and survival outcomes of this locally advanced/metastatic ES population are relatively poor. The clinical testing of novel agents remains a high priority.

Legal entity responsible for the study: EORTC

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1497P Efficacy and safety of patients treated long-term with trabectedin (t) on the expanded access program: A retrospective analysis

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Background: Treatment of soft tissue sarcoma (STS) with long-term systemic therapy can be limited by cumulative toxicity. Treatment with T for prolonged courses without the cumulative toxicity has been previously described from clinical trials. Here we report the efficacy and safety for patients (pts) treated long term (≥ 6 months) in a real world setting in the T Expanded Access Program from 2005-2010.

Methods: In this retrospective analysis of pts with pre-treated, relapsed/refractory STS of multiple histologies treated ≥6 mo with T (1.5 mg/m2 iv q3wk), we compared pts treated 6-12 mo and >12 mo.

Results: Of 1803 pts, 401 (21.6%) remained on treatment ≥6 mos; 268 (14.5%) for 6-12 mo and 133 (7.2%) >12 mo. Demographics did not differ. Leiomyosarcoma or liposarcoma were the most common histologies. The mOS (mo) was 18.1 and 47.0, ORR was 7.8% and 6.8%, and clinical benefit rate (CR+PR+SD) (95%CI) was 47.4% (41.3;53.6) and 38.3% (30.1;47.2) in the 6-12 mo and >12 mo groups, respectively. The incidence of adverse events (AE)s and serious adverse events (SAE)s were similar in both groups (Table). The most common grade 3/4 AEs occurring in ≥ 5% were neutropenia, thrombocytopenia, anemia, ALT/AST increase, fatigue and nausea. A majority received dose reduction or delay; the primary reason for treatment discontinuation was disease progression. The longest observed duration of treatment was 55 mo (64 cycles; synovial sarcoma) and 54 mo (73 cycles; uterine leiomyosarcoma).

Table: 1497P Safety and Efficacy

	6-12 Months (N = 268)	>12 Months (N = 133)
Median Treatment Duration (mo), range	8.4(6; 12)	16.3 (12; 55)
Treatment Response,		
Complete response, n (%)	1 (0.4)	3 (2.3)
Partial response, n (%)	20 (7.5)	6 (4.5)
Stable disease, n (%)	106 (39.6)	42 (31.6)
Progressive disease, n (%)	20 (7.5)	12 (9.0)
Not available, n (%)	121 (45.1)	70 (52.6)
Treatment-emergent adverse events (TEAEs)	225 (84.0)	119 (89.5)
Serious TEAEs	88 (32.9)	47 (35.3)
Treatment discontinued	255(95.1)	103 (77.4)
Due to disease progression	192(71.6)	72 (54.1)
Due to adverse event	10 (3.7)	2 (1.5)
Patients with cycle delay	154 (57.5)	82 (61.7)
Patients with dose reduction	172 (64.2)	104 (78.2)

Conclusions: T can be safely administered and well tolerated in pts who receive a prolonged duration (≥6 mo) of therapy. Improved mOS may be achieved in pts who experience prolonged disease stabilization following T but adjustments in dose or schedule is frequently required.

Clinical trial identification: NCT00210665

Legal entity responsible for the study: Janssen Research & Development, LLC

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1498P Efficacy and safety of trabectedin in an elderly patient subgroup (≥65 years) with advanced leiomyosarcoma (LMS) or liposarcoma (LPS) from the Expanded Access Program (EAP)

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Background: Elderly patients (pts) (≥65 yrs) with soft tissue sarcoma may have limited treatment options due to increased comorbidities and toxicities from available therapeutic agents. Previous retrospective analyses have suggested that trabectedin (T) has similar safety and efficacy outcomes irrespective of pt age.

Methods: In this multicenter, open-label study, pts received IV T (1.5 mg/m2) every 3 wks. We retrospectively analyzed the efficacy and safety of T in pts ≥65 yrs treated from 2005-2010 on this EAP.

Results: Mean age was 71 and 49 in the ≥65 (n = 350) and <65 (=1453) groups respectively. Pt demographics and disease characteristics were similar in ECOG score, race, gender, and histology. Median duration of therapy was 3 cycles in both groups. Pts receiving prolonged therapy (>12 mo) was 26 (7.4%) and 107 (7.4%) in the ≥65 and <65 groups, respectively. Elderly patients treated with T experienced similar median OS, ORR, and CBR (Clinical Benefit Rate, CR+PR+SD) compared to the <65 group with a median OS of 11.5 mo and 12.3 mo, ORR of 7 (3.9%) and 41 (5.4%), and CBR of 78 (43.1%) and 313 (40.1%) in the in the ≥65 and <65 groups, respectively. Toxicities in the elderly group were consistent with previously reported safety profiles, and incidence in the elderly group were comparable to those of the <65 group. Treatment-emergent adverse events (TEAEs), and serious TEAEs were similar in both groups. The percentage of pts requiring dose reduction and dose delay in pts who received ≥2 cycles was also similar with 96 (33.6%) and 444 (36.2%) of pts requiring dose delay and 135 (47.2%) and 563 (46.0%) requiring dose reduction in the ≥65 and <65 groups, respectively. In both groups, the majority of pts discontinued treatment due to disease progression with only 32 (9.1%) and 118 (8.1%) of pts discontinuing treatment due to an AE in the >65 and <65 groups, respectively.

Conclusions: The efficacy and safety profile of T in pts ≥65 was similar to that observed in pts <65 in this EAP. Based upon this real world experience, T should be considered as a treatment option for elderly pts with soft tissue sarcoma and good performance status irrespective of age.

Clinical trial identification: NCT00210665

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1499P The routine real-life use of trabectedin (T) in patients with advanced soft tissue sarcoma (STS) across Europe: An analysis of overall vs. per country results from Y-IMAGE study

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Background: The prospective, non-interventional, phase IV Y-IMAGE study evaluated the use of T in real-life clinical practice across Europe in patients with advanced STS.

Methods: Data from adult STS patients treated with T 1.5 mg/m^2 given as 24-h i.v. infusion q3w were collected. Patients must have received at least 1 cycle of T and currently be on T treatment. The primary endpoint was progression-free survival (PFS) as defined by investigators. The analyses were conducted in the overall population (OP)

Table: 1499P

	Full analysis set, n (%)				
	France (n = 26)	Germany (n = 29)	Italy (n = 69)	UK (n = 26)	Overall population (n = 218)
Age at study entry (years); Median (range)	58.5 (22-77)	58 (23-79)	59 (26-79)	56.6 (25-73)	58.0 (21.0-79.0)
Female	15(57.7)	15 (51.7)	44 (63.8)	13 (50.0)	123 (56.4)
Histology (≥10% of patients)					
Leiomyosarcoma	11 (42.3)	11 (37.9)	29 (42.0)	16 (61.5)	92 (42.2%)
Liposarcoma	5 (19.2)	–	23 (33.3)	7 (26.9)	51 (23.4)
Synovial sarcoma	4 (15.4)	5 (17.2)	–	–	23 (10.6%)
Cycles per patient Median (range)	5.5 (2-29)	6.0 (2-18)	6.0 (1-30)	10.5 (1-44)	6.0 (1-44)
Cumulative dose received mg/patient	12.1 (3.7-48.2)	20.8 (5.6-51.0)	14.3 (1.9-60)	26.2 (3-116.4)	14.7 (1.8-116.4)
Cycle duration (days)	24.9 (21-41)	26.8 (21-44.4)	23.7 (20.5-32.5)	24.2 (21-30.6)	24.1 (20-47.5)
Dose intensity (mg/m^2/week)	0.7 (0.2-1.0)	0.6 (0.4-1.1)	0.6 (0.3-1.0)	0.7 (0.5-1.0)	0.7 (0.2-1.1)
Median PFS (months) [95% Confidence interval]	7.6 [3.3-NR]	5.9 [3.4-11.2]	6.8 [3.4-10.2]	8.3 [5.5-11.4]	5.9 [4.9-7.8]
Objective response rate (ORR) (Complete + partial response) [95% Confidence interval]	6 (23.1) [9.0-43.6]	9 (31.0) [15.3-50.8]	15 (21.7) [12.7-33.3]	10 (38.5) [20.2-59.4]	58 (26.6) [20.9-33.0]
Disease control rate (DCR) (ORR + stable disease) [95% Confidence interval]	17 (65.4) [44.3-82.8]	20 (69.0) [49.2-84.7]	48 (69.6) [57.3-80.1]	22 (84.6) [65.1-95.6]	143 (65.6) [58.9-71.9]
Time to progression (TTP), median (months) [95% Confidence interval]	7.8 [4.9-NR]	6.9 [4.2-11.2]	6.8 [3.4-10.2]	8.3 [5.5-11.4]	5.9 [4.9-8.1]
Overall survival (OS), median (months) [95% Confidence interval]	20.3 [9.6-NR]	27.3 [9.2-NR]	22.5 [19.0-NR]	20.0 [18.2-23.6]	21.3 [18.8-24.3]
Growth modulation index (GMI), median [a] Range (min-max) ≤1.1, n (%) >1.1 - <1.33, n (%) ≥1.33, n (%)	0.7 (0.1-16.3) 15 (65.2) 1 (4.3) 7 (30.4)	0.9 (0.0-15.0) 12 (50.0) 2 (8.3) 10 (41.7)	0.7 (0.0-16.7) 35 (62.5) - 21 (37.5)	2.3 (0.1-15.4) 11 (42.3) - 15 (57.7)	0.8 (0.0-42.5) 110 (56.1) 10 (5.1) 76 (38.8)

[a]The GMI (TTP trabectedin/TTP prior chemo) was assessed on 196 patient: France, n = 23; Germany, n = 24; Italy, n = 56; UK, n = 26. NR, not reached.

and separately in countries with the highest recruiting rate to cover inter-country variations: France (F), Germany (G), Italy (I) and the UK.

Results: A total of 218 patients from 41 centers and 9 European countries were evaluated. Demographics and baseline characteristics of patients recruited in the 4 countries of interest were well-balanced and comparable to those observed in OP. Patients received a median of 6 cycles of T (range: 1-44), mostly on an outpatient basis (n = 132; 60.6%). Across all centers the median cycle duration, and median dose and dose intensity were similar to those observed in OP. Analysis of PFS data showed a similar outcome in G (median PFS: 5.9 months) to that observed in OP (5.9 months), and a rather higher PFS in the UK (8.3 months), F (7.6 months) and I (6.8 months). The patients from the UK received the highest median number of cycles (10.5) and cumulative dose of T (26.2 mg) as compared to F, G and I. This was associated with favorable efficacy outcomes in those patients, particularly in terms of improved PFS (8.3 months), responses (ORR: 38.5%; DCR: 84.6%) and a high growth modulation index of 2.3. T treatment resulted in a comparable median overall survival in all patients (21.3 months), being somewhat larger among patients treated in sites across G (27.3 months). Febrile neutropenia (2.3% of patients), neutropenia, nausea, and pneumonia (1.4% each) were the most common T-related grade 3/4 adverse drug reactions.

Conclusions: In real-life setting T confers meaningful benefits to patients with multiple STS histotypes with a manageable safety profile regardless of small country variations.

Clinical trial identification: Y-IMAGE; ET-D-020-12

Legal entity responsible for the study: PharmaMar

Funding: PharmaMar

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1501P Safety and efficacy of pazopanib (PAZ) in advanced soft tissue carcinoma (aSTS) by prior lines of therapy, age, and dose modifications: PALETTE subgroup analyses

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Background: PALETTE was a randomized phase 3 trial (NCT00753688) that demonstrated single-agent activity of PAZ in advanced STS (aSTS). We evaluated the relationship between age, prior lines of therapy, and dose modifications on the safety and efficacy of PAZ in aSTS.

Methods: Median progression-free survival (mPFS) was evaluated in subgroups of prior lines of therapy (1 prior line; 2+ prior lines), age (<65 y; ≥65 y), and dose reductions and interruptions (no dose reduction/interruption; ≥1 dose reduction/interruption). Adverse events (AEs) were also compared in subgroups of prior lines of therapy and age. All analyses were descriptive and exploratory and require cautious interpretation.

Results: A total of 246 patients received pazopanib in the PALETTE study. Median PFS and median overall survival (OS) were longer in patients receiving PAZ who had only 1 prior line of therapy vs 2+ prior lines of therapy (mPFS, 24.7 vs 18.9 weeks [Table]; OS, 13.7 vs 11.3 months). In patients receiving PAZ, mPFS was similar in ages <65 and ≥65 y (20.0 and 20.1 weeks, respectively). In patients receiving PAZ, mPFS was maintained in patients requiring dose reductions or dose interruptions to manage toxicities

(Table). Regardless of number of prior lines of therapy, patients receiving PAZ had similar AE rates. The AEs leading to study discontinuation in patients receiving PAZ were higher in ≥ 65 vs < 65 y group (30% vs 17%, respectively). Rates of dose reductions, dose interruptions, and serious AEs leading to study discontinuation were similar between the 2 age groups.

Table: 1501P

Subgroups	N	Pazopanib, mPFS, weeks (95% CI)
Lines of therapy		
1 prior line	110	24.7 (19.6-27.4)
2+ prior lines	136	18.9 (11.9-20.1)
Age		
<65 y (range: 18-64)	184	20.0 (17.9-22.0)
≥65 y (range: 65-83)	62	20.1 (11.7-31.6)
Dose reduction		
No dose reduction	154	11.9 (8.9-19.3)
≥1 dose reduction	92	27.7 (21.1-35.7)
Dose interruption		
No dose interruption	107	11.0 (8.1-19.3)
≥1 dose interruption	139	21.3 (20.1-27.7)

mPFS, median progression-free survival; CI, confidence interval

Conclusions: Longer mPFS was observed in patients receiving PAZ following only 1 line of therapy. Additionally, mPFS with PAZ was maintained regardless of patient age or if dose modification was required to manage toxicity.

Clinical trial identification: NCT00753688

Legal entity responsible for the study: Novartis Pharmaceutical Corporation

Funding: Novartis Pharmaceutical Corporation

Disclosure: A. Le Cesne: Pharmamar, Lilly, Pfizer, Novartis, Amgen. S. Bauer: Research support: Novartis, Blueprint Medicines, Ariad. Ad board: GSK, Novartis, Pfizer, Bayer, Fresenius, Lilly, Blueprint Medicines, Deciphera. CME-Honoraria: Pharmamar, GSK, Bayer, Novartis. Travel support: Pharmamar, Bayer. G.D.S. Demetri: Grants and personal fees from Novartis, during the conduct of the study; grants and personal fees from Janssen, Eisai, Eli Lilly and PharmaMar, outside the submitted work. W.T.A. van der Graaf: Research grants: GSK, Novartis. Advisory board: Bayer. G. Han, L. Dezzani, Q. Ahmad: Employee of Novartis. H. Gelderblom: Grants to institution LUMC, during the conduct of the study.

1502P Evolution in neutrophil-to-lymphocyte ratio (NLR) among advanced soft tissue sarcoma (STS) patients treated with pazopanib within EORTC 62043/62072 trials

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Background: A high NLR has been shown to be associated with a poor prognosis in several solid tumors including STS and might be helpful for patient stratification and individual risk assessment. The aims of this study were to confirm that higher NLR at baseline is associated with worse prognosis in STS and to evaluate if an early decline of NLR during treatment with pazopanib is associated with a more favorable prognosis.

Methods: The single-arm phase II EORTC 62043 and placebo-controlled phase III EORTC 62072 were both investigating the effect of pazopanib in patients with advanced STS. We evaluated NLR at baseline and 50 days later. Multivariate analyses on pazopanib-treated patients investigated the prognostic value on both Progression-Free Survival (PFS) and Overall Survival (OS) of NLR at baseline as well as the predictive value of changes in NLR from baseline to the 50-days landmark. Sensitivity analyses were conducted on the placebo-treated patients.

Results: Among the 333 eligible patients treated with pazopanib, a NLR at baseline ≥3 was associated with shorter PFS and OS in comparison to NLR <3 (HR 1.44; 95% confidence interval {CI} = 1.14-1.82; p-value 0.002 and HR 1.86; 95% CI = 1.43-2.41; p-value <0.001, respectively). Changes in NLR ratio were defined as a difference of at least 40% with baseline. Compared with no changes, an increase or decrease in NLR did not affect PFS (HR 1.19; 95% CI = 0.71-1.98 and HR 0.94; 95% CI = 0.71-1.24; p-value 0.685, N = 262 patients) or OS (HR 1.40; 95% CI = 0.90-2.16 and HR 0.96; 95% CI = 0.7 2- 1.28; p-value 0.255, N = 302 patients). Thresholds other than 40% difference to define NLR change did not impact the result and no association between changes in NLR and outcome was seen in placebo-treated patients. The median NLR change in patients treated with pazopanib was a decrease of 30.4% compared to an increase of 14.5% in placebo.

Conclusions: In this study, limited by its retrospective design, the prognostic value of NLR at baseline was confirmed in advanced STS patients, irrespective of treatment. Changes in NLR during the first 50 days of treatment with pazopanib were not associated with patient outcome and can therefore not be used as an early marker for response.

Legal entity responsible for the study: EORTC

Funding: EORTC STBSG

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1503P Benefit of the use of tyrosine kinase inhibitors (TKIs) in patients (pts) with METAstatic Soft Tissue SARComa (STS) in a Real-Life Setting: an ancillary analysis of the METASARC Study

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Background: Treatment options for pts with advanced STS are limited. STS, like other proliferating malignancies, are dependent on the formation of new blood vessels to support their growth, invasion and metastasis. Growth Modulation Index (GMI) has been demonstrated as a relevant endpoint to assess clinical in patients with advanced STS. There are no data related to GMI in STS patients treated with anti-VEGFR targeted therapy.

Methods: Pts with metastatic STSs diagnosed between 1990 and 2013 and documented in the prospectively maintained database of the French Sarcoma Group who have received at least one TKI during their treatment were analysed. GMI, defined as the ratio of the Time To Progression (TTP2) under the TKI/TTP under the previous line of treatment (TTP1) was calculated.

Results: 209 pts (102 male) were included in this study. Median age was 50 (11-83). 234 lines of TKI were administrated. The drugs used were: Pazopanib (77, 33%), Sorafenib (70, 30%), Sunitinib (45, 19%), Regorafenib (30, 13%), Others (12, 5%). The most frequent histology subtypes were: leiomyosarcoma (64, 30.6%), undifferentiated sarcoma (28, 13.4%), synovialosarcoma (20, 9.6%), desmoplastic round cell tumor (14, 6.7%) and angiosarcoma (11, 5.3%). Median of previous lines was 2 (0 – 4). Median TTP under TKI was 4.1 months (0 – 131.1). GMI was available for 201 pts. Median GMI was 0.76 (0.02 - 12.49). GMI was ≥ 1 in 87 (41.6%) pts and ≥ 1.3 in 65 (31.1%) pts. 17 pts received 2 consecutive lines of TKI. For these pts, median GMI (TTP under TKI2/TTP under TKI1) was 1 (0.12 – 8.77). Seven (41.2%) had a GMI ≥ 1.3.

Conclusions: Targeting VEGFR was associated with significant clinical benefit (GMI ≥ 1.3) in about one third of STS pts. Up to 41% of patients progressing on a TKI experienced clinical benefit with another TKI suggesting the lack of absolute cross-resistance between TKI.

Legal entity responsible for the study: French Sarcoma Group

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1504P Response to apatinib in advanced alveolar soft part sarcoma

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Background: Alveolar soft part sarcoma (ASPS) is a rare, hypervascular and chemoresistant soft tissue sarcoma. Apatinib, a novel tyrosine kinase inhibitor that highly selectively binds to the ATP-binding site of VEGFR-2 within cells resulting in inhibition of tumor angiogenesis, has shown a substantial potential in angiosarcoma, malignant fibrous histiocytoma and round cell liposarcoma. This study aimed to review the clinical efficacy and safety of apatinib in ASPS.

Methods: The clinical information of 6 patients with advanced ASPS who received apatinib were collected. The median age of them was 26.5 years old (17y-32y). Five patients were found with multiple lung metastases and one (case 4) was with locally advanced unresectable tumor. The maximum diameters of locally advanced tumor and metastatic nodules were measured by MRI and thin-section CT, respectively. All cases received apatinib at initial continuous daily dosing of 500 mg every 4 weeks. Clinical efficacy was evaluated according to RECIST v1.1. The adverse events (AEs) were graded according to CTCAE v4.03.

Results: Median follow-up from start of apatinib treatment was 10.2 months (range, 1-21 months). Five of 6 patients who received at least 1 complete cycle of apatinib treatment were eligible for the efficacy analysis (Table). One patient achieved RECIST complete response and stop apatinib treatment after six cycles. Four patients got partial response. No disease progression was found. The current objective response rate to apatinib treatment was 100% (5/5). The most common grade 3/4 treatment-related AEs were hand-foot syndrome (60.0%), hypertension (20.0%), and hepatotoxicity (20.0%). No drug-related severe AEs occurred. At the time of analysis, all patients were still alive and five patients continued to receive apatinib.

Conclusions: Our analysis confirms the short-term efficacy and safety of apatinib in patients with advanced ASPS. This result supports future randomized controlled trial to further verify anti-tumor activity of apatinib in stage IV sarcomas.

Legal entity responsible for the study: Chongqi Tu

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1505P Analysis of expression of immunomodulation factors in alveolar soft-part sarcoma: a retrospective study from the Spanish Group for Research on Sarcoma (GEIS)

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Background: Alveolar soft-part sarcoma (ASPS) is an exceedingly rare entity. We previously reported on a series of 12 ASPS the expression of PD-1/PD-L1 and lymphocytic infiltrates. PD-L1 staining was positive in 50% of the cases, suggesting a role for immunomodulatory interventions. We now enlarge the series and explore the expression of immune-related genes with the HTG EdgeSeq System and analyze their possible prognostic role.

Methods: Patients (pts) diagnosed with ASPS from Dec 1994 to Jul 2016 were reviewed. Clinical characteristics and outcome were collected. Immunohistochemical expression was tested on archived Formalin-Fixed Paraffin-Embedded (FFPE) blocks using PD-L1 (ab205921; Abcam), CD8 (ab4055; Abcam) antibodies. An ImmunOncology (IO) panel of 549 mRNAs was evaluated with the HTG EdgeSeq System from one 5µm FFPE section. This novel technology consists in a tissue digestion followed by a pre-hybridization with specific probes using quantitative nuclease protection assay (qNPA) and quantified by a standard RNA-seq protocol in a NGS sequencer.

Results: We identified 16 ASPS pts: median age 23y (6-62), M/F=5/11. Stage localized/metastatic in 11/5. With a median FU of 91 mos (4-151), 6/11 pts (54%) relapsed, with a median RFS of 19 mos (95% CI 1-75) and 2 pts died. PD-L1 was pos in tumor in 10/16 (62%) pts. HTG showed differential expression of immune-related genes according to stage (localized vs metastatic) in MNDA (log2 fold change: -3.01, $p < 0.00001$) and PRAME (log2 fold change: 1.9, $p < 0.0002$). Pts relapsing differentially expressed ABCC2 (log2 fold change -1,64, $p < 0.04$) when compared with those not relapsing. PD-L1 pos vs neg tumors (pos>5% membrane staining for PD-L1) differentially expressed TNFSF11 (fold change: -1,77, $p = 0.05$). Tumors infiltrated/not for CD8 lymphs (pos>10% of CD8) had a differential expression of CCL18 (log2 fold change: 4,89, $p < 0.0001$) and SLAMF7 (log2 fold change 2,37, $p < 0.0089$).

Conclusions: PD-L1 is expressed in more than a half of ASPS of our series. Differential expression in immune-associated genes suggest an immune related gene profile on this entity with clinical and pathological implications. Further exploration of immune-modulation in ASPS is ongoing.

Legal entity responsible for the study: Spanish Group for Research on Sarcoma

Funding: Spanish Group for Research on Sarcoma (GEIS).

Disclosure: All authors have declared no conflicts of interest.

1506P PD-L1 inhibition – a new therapeutic opportunity in cutaneous angiosarcoma?

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Background: Cutaneous angiosarcomas (cAS) represent a particularly challenging sarcoma subtype that frequently occurs in pretreated patients as a consequence of radiation therapy or chronic lymphedema. Local treatments are complicated as affected sites are often compromised by previous surgery and irradiation and tumor lesions lack a clear delineation. Novel treatments are therefore urgently needed to improve the outcome of these patients.

Methods: We identified 130 angiosarcomas from our institutional database of which 37 originated in the skin. Clinical characteristics and outcome was analyzed and available tumor tissue was tested for expression of PD-L1 and infiltration of immune cells, including CD8+ cells.

Results: Response to classical chemotherapeutic drugs was highest for taxanes, but frequent responses were also seen with liposomal doxorubicin, gemcitabine or oral cyclophosphamide. Despite promising chemotherapy responses, most patients eventually died of disease with often dismal local complications. Using IHC we observed several cases of cAS that showed a significant expression of PD-L1 between 10-20% on tumor cells. In addition, infiltration of immune cells with the presence of CD8+ cells was regularly observed. One of the patients with PD-L1-positive angiosarcoma of the scalp who had progressed after several lines of chemotherapy was treated with pembrolizumab. Following the second application the patient already showed a dramatic improvement of symptoms with complete healing of a large area of ulcerating and bleeding skin and ongoing remission after 6 months of treatment.

Table: 1504P Clinical data of six patients with alveolar soft part sarcoma who received apatinib

Case	Age/gender	Local tumor location	Local tumor size (cm)	Local tumor resection (Yes/No)	Chemotherapy	Cycles	Clinical efficacy
1	17/male	Left thigh	4.5	Yes	Gemcitabin + Docetaxel	Stop 6	CR
2	27/female	Right thigh	10.5	No	None	Ongoning 2	PR
3	29/male	Left thigh	11.3	No	Ifosfamide	Ongoing 4	PR
4	32/male	Right thigh	16.9	No	Ifosfamide+ Cisplatin	Ongoing 4	PR (Local tumor volume decrease)
5	26/male	Left thigh	9.6	Yes	None	Ongoing 6	PR
6	28/Female	Right thigh	5.8	No	None	Ongoing <1	–

Conclusions: Based on this study, PD-L1-directed therapy may represent a particular opportunity for angiosarcomas of the skin given the frequency of PD-L1 expression and infiltration of immune cells. Our findings suggest prospective immunotherapy studies in this sarcoma subtype.

Legal entity responsible for the study: Department of Medical Oncology, West German Cancer Center, University Hospital Essen, University of Duisburg-Essen, Essen, Germany

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1507P Pembrolizumab (PEM) in patients with advanced/metastatic bone sarcoma (BS) or soft tissue sarcoma (STS): Named patient use by the Medical University of Vienna

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Background: Treatment options in locally advanced/metastatic BS and STS are limited. PEM has shown first signs of promising activity in some histologic subtypes. In this named patient use BS and STS patients who either failed standard therapy or where no standard therapy was established were treated with PEM.

Methods: This retrospective analysis includes efficacy/safety data from 18 pts. with advanced/metastatic BS/STS treated with PEM 200mg d1, q21d between May 2016 and April 2017.

Results: 10 pts. were female (56%), 8 pts. male (44%). Median age was 45 yrs. (range 18-84 yrs.). Extent of disease at initial diagnosis was localized in 15 pts. (83%) and advanced/metastatic in 3 pts. (17%). The median number of previous lines of systemic treatment before PEM was 3 (range 0-7 lines). In total, 71 cycles of PEM were administered (median 3 cycles per pt., range 1-11 cycles). Immune-related side effects were hypothyroidism in two pts. and uveitis in one pt. PD-L1 assessment on tumor samples is ongoing.

Table: 1507P

patient ID	histology	n PEM cycles	status	status PEM
1	fibromyxoid sarcoma	4	*	1
2	OSA	11	0	0 NED
3	fibrosarcoma	3	*	1
4	myxofibrosarcoma	8	0	0 PR
5	myxofibrosarcoma	2	*	1
6	angiosarcoma	3	0	1
7	dedifferentiated LPS	7	0	0 PR
8	EMC	3	0	1
9	EMC	3	0	1
10	chondrosarcoma	5	0	0 SD
11	myxoid LPS	3	0	0 PR
12	angiosarcoma	1	*	1
13	dedifferentiated LPS	5	0	0 SD
14	synovialsarcoma	3	0	0 SD
15	epitheloid sarcoma	3	0	0 PR
16	OSA	2	0	0 ie
17	OSA	3	0	0 ie
18	myxoid LPS	2	0	0 ie

Abbreviation: OSA = osteosarcoma, EMC = extraskeletal myxoid chondrosarcoma, LPS = liposarcoma, status 0 = alive, * = dead; status PEM 0 = PEM ongoing, 1 = PEM discontinued to PD (progressive disease); NED = no evidence of disease, PR = partial remission, SD = stable disease, ie = response in evaluation.

Conclusions: In this unselected cohort, PEM seems to have some activity in advanced/metastatic BS/STS. However, longer follow up of treated patients and prospective clinical trials of PEM in BS/STS patients will define the value of PEM in this patient cohort. Updated efficacy and toxicity data as well as PD-L1 expression levels will be presented at the meeting.

Legal entity responsible for the study: Thomas Brodowicz, Clinical Division of Oncology, Medical University of Vienna

Funding: None

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1509P Characteristics and prognosis of gastrointestinal stromal tumor in the pre-imatinib era: An analysis based on the Kinki GIST registry in Japan

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Background: Recent breakthroughs regarding the oncogenesis of gastrointestinal stromal tumor (GIST) have led to the wider use of imatinib (IM). In addition, since perioperative IM has been established, more accurate information regarding the clinical behavior of GIST is mandatory. However, there is no big data about the clinicopathological characteristics and prognosis of GIST in Japan. The aim of this study was to clarify them based on an analysis of the GIST registry conducted by the Kinki GIST Study Group in Japan.

Methods: The registry was designed to collect data on background characteristics, treatment methods, pathologic characteristics, and prognosis of primary GIST from 2003 through 2007 at 40 participating institutions.

Results: The study enrolled 346 male patients and 332 female patients. The median [range] age was 66 [18-93] years. The primary sites were stomach (74%), small intestine (19%), rectum (3%), esophagus (1%), colon (1%), and others (1%). Fifty-eight percent were asymptomatic and 42% were symptomatic e.g. bleeding (17%), pain (10%), and digestive symptoms (9%). None of the patients was received perioperative IM therapy. Pathological examination revealed that the tumor size was 4.0 [0.1-35]cm and the mitotic count was 3 [0-300] per 50 high-powered fields. There were 91.0% KIT positive GISTs and 82.9% CD34 positive GISTs. Ninety-seven (14.5%) patients showed recurrence and the common recurrent sites were liver (n = 58) and peritoneum (n = 33). According to the modified-Fletcher criteria, the recurrence rates were 0% (0/93, very low-risk group), 2.6% (6/230, low-risk,), 4.6% (4/87, intermediate-risk), and 38.9% (75/193, high-risk), respectively. The 5-years overall survival rate was 89.0%. The 5-years recurrent free survival rate (RFS) of gastric GISTs was significantly better than that of other sites' GISTs (5-years RFS:82.7% vs. 63.9%, $P < 0.001$).

Conclusions: We reported the clinicopathological characteristics of GIST in multicenter registry study in Japan. Currently applied GIST risk classification system is comparable to predict high- or low-risk patients with primary non-metastatic and completely resected GIST in pre-IM era.

Legal entity responsible for the study: Kinki GIST registry

Funding: Kinki GIST registry

Disclosure: All authors have declared no conflicts of interest.

1510P Early response evaluation by 18F-FDG-PET influences management in gastrointestinal stromal tumor patients treated with neo-adjuvant intent

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Background: Early response evaluation by ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) is effective in gastrointestinal stromal tumors (GISTs) treated with imatinib and recommended in GISTs treated with neo-adjuvant intent. Yet, it is unclear whether this effects treatment decisions.

Methods: All patients in the Dutch GIST Registry treated with imatinib with neo-adjuvant intent were identified. Only FDG-PETs made within 8 weeks after initiation or change (in dose or switch) of imatinib were included. Responses were derived from radiological reports and defined in 3 categories: 1) complete response; 2) partial response; 3) no response. Change in management was defined as a difference between pre-PET and post-PET treatment plans. Four categories were defined: change in 1) surgical management; 2) systemic treatment; 3) treatment objective (from curative to palliative); 4) management regarding a second tumor.

Results: Seventy FDG-PETs for early response evaluation in 63 patients treated with neo-adjuvant intent were identified. Forty-one patients (65.1%) had a KIT exon 11 and 22 (34.9%) had a non-KIT exon 11 mutation (15 other and 7 unknown mutations). Of the 70 scans 64 (87.1%) had a baseline, 50 (71.5%) showed metabolic response (partial and complete), and 18 (25.7%) led to change in management. Change in management was strongly correlated with a lack of response ($p < 0.001$) and a non-KIT exon 11 mutation ($p < 0.001$). Mutational status and response were strongly correlated ($p < 0.001$). Out of 29 FDG-PETs conducted in non-KIT exon 11 GISTs, 15 (51.7%) led to change in management: 1 (3.4%) in surgical management, 6 (20.7%) in systemic treatment, 7 (24.1%) in both and 1 (3.4%) regarding a second tumor. Out of 51 FDG-PETs conducted in KIT exon 11 GISTs, change in management was seen 3 times (5.9%): twice in systemic treatment (dose increase after partial response was seen) and once regarding a second tumor. No change in treatment objective was seen.

Conclusions: In contrast to GIST patients harboring a KIT exon 11 mutation, in non-KIT exon 11 mutated GISTs treated with neoadjuvant intent early response evaluation by FDG-PET often leads to change in management.

Legal entity responsible for the study: Neeltje Steeghs

Funding: Novartis, Pfizer and Bayer

Disclosure: N. Steeghs: Research grant for the Dutch GIST Registry from Novartis, Pfizer and Bayer. All other authors have declared no conflicts of interest.

1511P Surgery in the treatment of metastatic and recurrent Gastrointestinal Stromal Tumors

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Background: Gastrointestinal stromal tumors (GISTs) are the most frequent mesenchymal tumors of the gastrointestinal tract. Surgery is the method of choice in treatment of localized GISTs but it also plays a great role in the treatment of advanced forms. The main goal of our study is to define the role of surgery for locally advanced and metastatic/recurrent lesions.

Methods: We have performed a retrospective analysis from a prospectively documented database. All histologically proven GISTs, diagnosed and treated between 2003 and 2016, were enrolled from 4 clinics in Saint-Petersburg, Russia. Cases of recurrent or metastatic GISTs were selected from the registry, and baseline characteristics and survival outcomes were analyzed. Patients were classified into two groups. The surgical treatment group (ST group) included those who underwent surgical treatment in addition to tyrosine kinase inhibitor (TKI) therapy after recurrence or metastasis, whereas the drug treatment group (DT group) included those who were treated only with TKI therapy.

Results: Metastasis or recurrence developed in 34 (22,8%) of the 149 patients with GISTs who had undergone surgery for primary localized or locally advanced tumors, 13 (38,2%) of whom were assigned to the ST group and 21 (61,8%) to the DT group. Median follow-up was 68 (4-162) months. In the ST group the 3-year overall survival rate (OS) was significantly higher than in DT group (92,3 vs. 61,9%, $p < 0,05$) but these groups didn't differ with respect to the 5-year overall survival rate (61,5 vs. 52,4%, $p > 0,05$). Median time to progression (TTP) was 23,9 months in the DT group and 29,7 months in the ST group ($p > 0,05$). OS was correlated with the pattern of recurrence: local-regional recurrence *vs.* distant metastasis – 3-year OS (94,4 vs. 50%, $p < 0,05$), 5-year OS (77,8 vs. 31,25%, $p < 0,05$). Median TTP didn't differ in both groups (18,5 vs. 20 months, $p > 0,05$).

Conclusions: Continuous TKI therapy appears to be important primarily for the prognostic improvement of patients with recurrent/metastatic GISTs. Surgical resection may have benefits when combined with TKI therapy for patients with stable disease or disease responsive to TKI therapy especially in the cases of local-regional recurrence.

Legal entity responsible for the study: Orlova Rashida

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1512P Clinicopathologic features and long-term follow-up of metastatic gastrointestinal stromal tumor (GIST) patients (pts) with durable response (≥ 5 years) to frontline imatinib (IM): A case-control study from GEIS

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Background: IM achieves disease control in most metastatic GIST pts, typically about 18 months. Interestingly, ∼15% GIST pts remain on IM beyond 5 years of continuous treatment. To date, clinicopathologic features predictive of long-term benefit to IM remain largely unknown.

Methods: We analyzed clinical, pathological and molecular characteristics, and long-term outcomes in metastatic GIST pts treated with continuous daily dosing of frontline IM in a cohort of pts benefiting ≥ 5 years, compared with a control group obtained from a national GEIS database.

Results: We found 41 IM long-term responders (IM-LTR) and 71 control cases (CC) with a median time on IM of 90.6 and 18.2 months, respectively. Compared to CC, IM-LTR were younger (59 vs 64 years, $p = 0.040$), fitter at diagnosis (performance status (PS) 0-1: 100% vs 82.2%, $p < 0.001$), had fewer metastasis prior to IM initiation (2.6 vs 7.5, $p < 0.001$), and primary tumors were bigger (10.4 vs 9 cm, $p = 0.005$) but had lower mitotic count (5.5 vs 15 per 50HPF, $p = 0.005$). There were no differences in terms of primary tumor location, disease status or metastases location at diagnosis. Mutational profile from IM-LTR (KIT ex 11, 81%; KIT ex 9, 0%; PDGFRA, 8%; wild-type, 11%) did not differ significantly from CC. IM-LTR had significantly better response pattern (complete response 34.1%; partial response 43.9%; stable disease 22%) and overall survival (not reached) over CC (9.2%, 40%, 26.2%; and 63 months, respectively). Only 7 pts (18%) receiving IM ≥ 5 years withdrew IM due to progression (69% CC, $p < 0.001$). Eight pts (25%) developed ≥ 1 new toxicities after ≥ 5 years on continuous IM; only 1 pt withdrew IM due to toxicity (grade 3 anemia). Univariate analyses show that pts with better PS ($p = 0.002$), low mitotic count ($p = 0.025$), low number of metastases ($p < 0.001$), and better response to IM ($p < 0.001$) achieve durable benefit from frontline IM.

Conclusions: Clinical and inherently biological tumor characteristics define a subset of GIST pts with increased likelihood to achieve durable benefit from IM. Molecular studies are needed to better identify these pts at treatment initiation.

Legal entity responsible for the study: Spanish Group of Sarcoma Research (GEIS)

Funding: Spanish Group of Sarcoma Research (GEIS)

Disclosure: All authors have declared no conflicts of interest.

1513P Tumor growth rate analysis of progression-free survival (PFS) and overall survival (OS) for patients with metastatic and/or unresectable gastrointestinal stromal tumors (GIST) receiving placebo or regorafenib in the phase 3 GRID trial

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Background: In the randomized, controlled phase 3 GRID trial (NCT01271712), regorafenib (REG) significantly improved PFS versus placebo (PBO) in patients with advanced GIST (HR 0.268; $P < 0.0001$). Here we report an analysis exploring prognostic characteristics of early tumor growth rate (eTGR) for PFS and OS.

Methods: The primary endpoint of GRID was PFS; OS was a secondary endpoint. Target lesions were assessed by central radiologic review based on RECIST (v1.1). Changes in target lesions over time were approximated by a parabola-like 3-parametric model. eTGR was defined as the percentage change per month of the sum of target lesion diameters from the start of double-blind treatment. To explore the association between eTGR and PFS and OS, values of eTGR were split into quartiles (Q) separately by treatment arm. PFS (cut-off in 2012) and OS (cut-off in 2015) were compared in each subgroup population by median times derived from Kaplan–Meier curves and from modeling with a Weibull distribution.

Results: For PBO and REG, there is a nearly inverse relationship between eTGR and median times of PFS and OS from Q1 to Q4 eTGR. For the REG subgroup in Q1 eTGR, this trend is lost, as it has similar or worse median times than the subgroups around zero eTGR, which show the best prognosis.

Table: 1513P

	PBO				REG			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Mean eTGR	–0.063	0.064	0.147	0.279	–0.128	–0.022	0.024	0.135
Median PFS*	2.7	1.5	1.0	0.8	5.5	7.8	6.0	1.6
Median OS*	45.5	21.8	12.3	9.7	29.1	28.9	17.4	11.5

*By Weibull model of Kaplan–Meier curves; durations in months.

Conclusions: In this exploratory analysis, stabilization of tumor lesions at treatment start seems to be prognostic for better PFS and OS outcomes. A strong reduction of eTGR, which is seen for some REG patients, is not necessary for further disease stabilization and improvement. eTGR may be an additional efficacy parameter to consider when monitoring REG and other tyrosine kinase inhibitor (TKI) treatments in TKI-resistant GIST.

Clinical trial identification: NCT01271712

Legal entity responsible for the study: Bayer

Funding: Bayer

Disclosure: C. Kappeler, A. Wagner: Employment and Stock Ownership: Bayer AG. G.D.S. Demetri: Consulting/Advisory Role: Bayer, Pfizer, Novartis, Eli Lilly, EMD Serono, Sanofi, Janssen Oncology, PharmaMar, Daiichi Sankyo, ARIAD, Blueprint Medicines, Kolltan Pharmaceuticals, WIRB-Copermicus Group, ZIOPHARM Oncology, Polaris, Nektar, Genocea Biosciences, G1 Therapeutics, Caris Life Sciences, Adaptimmune, Kyocera, Eisai; Stock Ownership: Blueprint Medicines, G1 Therapeutics, Bessor Pharma, Caris Life Sciences, Champions Oncology, N-of-One; Research Funding: Novartis, Pfizer, Bayer, AbbVie, Janssen Oncology, Eisai, Amgen; Leadership: Blueprint Medicines; Other: Patents licensed to Novartis from Dana-Farber, with royalty paid to Dana-Farber.

1514P Serum miRNA abundances discriminate imatinib-naive patients with advanced gastrointestinal stromal tumors (GIST) from those in remission on Imatinib therapy

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Background: Deregulation of microRNAs (miRNAs) expression is observed virtually in all major types of neoplasm and miRNAs level in blood circulation are investigated as a potential diagnostics or prognostics biomarkers for neoplastic disorders. Gastrointestinal stromal tumors (GISTs) is the most common sarcoma of the gastrointestinal tract and to date performed studies on GISTs have provided mounting evidence on altered miRNA association with clinical, pathological features and Imatinib resistance in GIST. However, the utility of circulating miRNA as response markers of GIST progression and for Imatinib treatment have not been evaluated

Methods: 36 metastatic or unresectable CD-117-positive GIST patients, were enrolled and serum sample was collected prior to Imatinib treatment. All patients responded initially to imatinib therapy. In 12 patients an additional serum sample was collected following targeted treatment at the time of remission. Control group comprised 30 healthy individuals. MiRNAs were isolated from serum with MirVANA miRNA Isolation Kit and then analyzed using deep sequencing on Ion Torrent PGM. Reads were mapped to miRBase miRNA collection with miRDeep2. Differential expression was evaluated with edgeR.

Results: Deep sequencing identified 1284 miRNAs. The pair-wise comparison between Imatinib treated and Imatinib-naive GIST samples uncovered 22 miRNAs with differential expression (adjusted p value <0.05) of which 10 (miR-142-5p, let-7d-3p, miR-30e-5p, miR-194-5p, miR-223-5p, miR-223-3p, miR-125a-5p, miR-199b-5p, miR-24-2-5p, miR-641) yielded AUCs (areas under Receiver Operating Characteristic curves) ranging 0.81 and 0.9, thus having a high discriminative properties. A comparison of imatinib-naive GIST and control healthy samples revealed 99 differentially expressed miRNAs (adjusted p value <0.05) of which four (miR-582-5p, miR-150-5p, miR-450b-5p, miR-450a-5p) reached AUCs with high discriminatory power ranging 0.81-0.84.

Conclusions: Circulating miRNA abundances can distinguish GIST patients from those in remission following Imatinib therapy as well as from the healthy controls. However, further studies evaluating the potential of designated microRNAs as response markers for treatment or as predictive markers of GIST are warranted.

Legal entity responsible for the study: Piotr Rutkowski

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1515P LncRNA H19, HOTAIR and MALAT1 as prognostic molecular biomarkers in GIST

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Background: Long non-coding RNAs (lncRNAs) are emerging as essential regulators of genetic and epigenetic networks. Their deregulation may underlie carcinogenesis suggesting their potential involvement in tumorigenic and metastatic processes, as well as their role as prognostic/predictive biomarkers for clinical use in patients with several solid tumors. Few studies evaluated lncRNAs expression in rare tumors such as Gastrointestinal Stromal Tumors (GISTs). Indeed, the upregulation of HOTAIR has been associated with tumor aggressiveness and metastasis, and poor survival of GIST patients. In order to gain more detailed insight on the molecular role of lncRNAs, we analyzed the expression levels of lncRNAs H19, MALAT1 and HOTAIR in tissue specimens of surgically resected GIST patients to evaluate the potential role of lncRNAs as prognostic biomarkers.

Methods: The expression of the lncRNAs H19, MALAT1 and HOTAIR was evaluated in a total of 40 pairs of disease formalin-fixed paraffin-embedded tissue and adjacent normal tissue from 40 GIST patients with localized and locally advanced disease using quantitative real-time reverse transcriptase.

Results: H19 was overexpressed in 50% GIST patients (p-value: 0.0496). MALAT1 was overexpressed in 45% GIST patients (p-value: 0.032). None of them had the related date with HOTAIR. Furthermore, the up-regulation of H19 has been found in 74% patients harboring cKIT mutations compared to 57% wild type patients (p-value: 0.042). Conversely the up-regulation of MALAT1 has been found in 76% patients harboring cKIT mutations compared to 100% wild type patients (p-value: 0.027). Finally, the up-regulation of H19 has been found in 100% patients with TTP < 3 months compared to 25% patients with TTP >3 months, while the up-regulation of MALAT1 has been found in 25% patients with TTP < 3 months compared to 75% patients with TTP >3 months.

Conclusions: H19 and MALAT1 appear upregulated in GIST patients according to the KIT- mutation status. These data would suggest a potential opposite prognostic value of both H19 and MALAT1 lncRNAs in these patients. The results of HOTAIR expression levels were indeterminated in all analyzed tumor samples, probably because HOTAIR has been degraded during its isolation. Further analyses are needed to confirm these data.

Legal entity responsible for the study: University of Palermo

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1516P Predictive factors of response to Sunitinib in metastatic Gastrointestinal Stromal Tumors (mGISTs): A retrospective analysis

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Background: Imatinib is currently the standard therapy for first line treatment of metastatic GIST. Although this treatment has demonstrated durable responses with PFS and OS benefit, most patients develop resistance and experience subsequent disease progression. Current treatment available in second line are Imatinib high-dose (800 mg/day) or Sunitinib. The presence of two options in this setting, in the absence of direct comparisons, raises many questions on the choice.

Methods: A total of 128 patients with metastatic GIST were collected in our analysis in this large database. We analyzed the validity of several parameters as possible predictors of response to treatment with Imatinib high-dose vs Sunitinib in patients progressing at the standard dose of Imatinib 400 mg/day. The parameters analyzed were: anatomic

site of primary GIST, site of metastasis, KIT and PDGFRa mutational status, and FDG-PET status at progressing disease. Every factor has been correlated with Progression Free Survival (PFS) for Imatinib 800 mg/day and Sunitinib treatment, measured in months. Datas collected have been analyzed with software "Medcalc", performed by using the Kaplan-Meier method.

Results: Univariate analysis showed Sunitinib more active then Imatinib in gastric GISTs (median PFS: Sun 12 months vs Ima 800 6 months; p < 0,0001), in pts with peritoneal metastasis (median PFS: Sun 10 months vs Ima 800 5 months; P = 0,2429), in wild-type (median PFS: Sun 20 months vs Ima 800 17 months; P = 0,1361) and PET-negative GIST patients (median PFS: Sun10 months vs Ima 800 7 months; p = 0,0874).

Conclusions: with the limitations of a retrospective analysis, this study identifies the gastric site of primary tumor as a predictive factor to efficacy of Sunitinib treatment in second line. The mutational status (GIST WT), the site of metastasis (peritoneum) and the FDG-PET status (negative), although not statistically significantly, seem to be elements of increased activity for Sunitinib treatment in second line.

Legal entity responsible for the study: University of Palermo

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1517P Analysis of PD-L1 Expression in Patients with Gastrointestinal Stromal Tumors

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Background: The immune system is believed to have an important role in solid tumor progression. The development of monoclonal antibodies targeting immune checkpoints, such as programmed cell death 1 (PD-1) and programmed cell death ligand 1 (PD-L1), have revolutionized the treatment of some cancers. Recent efforts have attempted to elucidate the relevance of the PD-1/PD-L1 pathway in gastrointestinal stromal tumors (GIST).

Methods: Formalin-fixed, paraffin-embedded specimens were obtained from resected GIST at Sunnybrook Health Sciences Centre between March 2008 and August 2015. PD-L1 analysis was based off a tissue microarray of the cases using the Roche Ventana SP263 antibody. Each case had 1mm cores taken from different areas of the tumor block. Normal controls used for PD-L1 were placenta and tonsil (epithelial and inflammatory). CD117 was assessed via immunohistochemistry in all tumor specimens.

Results: Of twenty-nine patients who underwent surgical resection, eight had insufficient tumor tissue for analysis, and three cases were excluded due to CD117 negativity after preoperative imatinib treatment, leaving 18 patients for analysis. Three of these 18 cases were positive for PD-L1 expression: 2 patients with moderate PD-L1 staining in 85% of the stromal cells and 1 with weak staining in 15% of the stromal cells. Fifteen patients were negative for PD-L1 expression. Analysis of PD-L1 expression in tumor-infiltrating lymphocytes was not feasible due to the lack of inflammatory cells in tumor environment. The patients whose samples had significant PD-L1 expression had gastric primaries, with tumour size <10cm. They did not require preoperative treatment, and did not have metastatic disease despite two having a high mitotic rate. The clinicopathologic characteristics of patients by PD-L1 expression status is demonstrated in Table 1.

Table: 1517P

	PD-L1 negative (N = 15)	PD-L1 positive (N = 3)
Age (± SD)	62 (14)	63 (14)
Gender M F	10 5	1 2
Location Gastric Small Bowel Colon Rectum	7 5 - 3	3 - - -
Metastasis No Yes	11 4	3 -
Preoperative Imatinib No Yes	7 8	3 -
Size (cm) Preoperative imatinib Upfront surgery	6.2 (1.3-16) 5.8(1.5-11)	– 9.5 (1.5-9.5)
Mitotic Rate (50 HPF) < 5 = or > 5	12 3	1 2

Conclusions: In this cohort, PD-L1 may be a favorable prognostic biomarker. Further studies to examine the clinical benefit of immunotherapy in GIST patients with or without PD-L1 expression are warranted.

Legal entity responsible for the study: Ana Beatriz Kinupe Abrahao

Funding: Glenita Mungcal GIST Research Award from the Life Raft Group Canada

Disclosure: All authors have declared no conflicts of interest.

1518P Gastrointestinal stromal tumors secrete Ghrelin and express ghrelin receptors – needs linguistic correction

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Background: Gastrointestinal stromal tumor (GIST) mainly occurs in the fundus ventriculi. Ghrelin is a multifunctional protein polypeptide, which can promote the occurrence and development of tumor. It is mainly produced in the fundus ventriculi. But the misdiagnosis rate and postoperative recurrence rate is high. This study was to determine the serum ghrelin level in the normal population, patients with GIST before and after operation. And The expression of ghrelin and its receptor was determined in GIST tissue and The expression of ghrelin in adjacent normal tissue in the same patient. We hope that ghrelin can provide a new idea for the diagnosis and prognosis of GIST.

Methods: Preoperative and postoperative serum of 78 patients with GIST and 69 normal persons was collected and determined the level of serum ghrelin by ELISA. Expression of ghrelin and ghrelin receptors in GIST tissue (47 cases) was determined and Expression of ghrelin in adjacent normal tissue was determined at same time by immunohistochemical. We observed whether there were statistically significant differences in statistical analysis.

Results: the average ghrelin in the serum of normal people was 20.14 pg/ml, and 31.25 pg/ml for GIST patients. P = 0.034. The mean value of serum ghrelin in 78 patients with GIST was 31.25 pg/ml before operation and 22.5 pg/ml after operation . P = 0.023. Ghrelin and its receptor expression positive rate was 100% in GIST (47 cases). Among them, Ghrelin: (+) 12%, (++) 29%, (+++) 38%, (++ ++) 20% Ghrelin receptors:(+) 4%, (++) 23%, (+++) 27%, (++ ++) 46% 4) The expression of ghrelin in tumor tissue was about 2.23 times than that of adjacent normal tissues.

Conclusions: Gastrointestinal stromal tumors secrete Ghrelin and express ghrelin receptors. Ghrelin may serve as an effective indicator for the diagnosis and prognosis of GIST.

Legal entity responsible for the study: Peking Union Medical College Hospital

Funding: Beijing Municipal Commission of Health and Family Planning

Disclosure: All authors have declared no conflicts of interest.

1519P Primary pleomorphic sarcoma (PS) and leiomyosarcoma (LMS) of bone: Retrospective analysis of an original series

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Background: To describe the clinico-pathological features of 23 patients affected by primary PS and LMS of bone, to confirm the diagnosis by molecular analysis, to evaluate the clinical outcome and to explore the prognostic impact of these features on disease-free (DFS) and overall survival (OS).

Methods: Primary PS and LMS of bone surgically treated from 2004 to 2015 were retrospectively reviewed. We analysed: age, sex, stage, histotype, histological-grade and surgical and/or medical therapy. IDH1 mutational status was evaluated and immunohistochemical staining was performed for smooth muscle actin and desmin. For molecular analysis tumor DNA was extracted from freshly cut FFPE sections by GeneRead^{TM} DNA FFPE (Quiagen) and ddPCR (Bio-rad) was used to determine the presence of IDH1H and IDH1C mutations. DFS and OS rates were calculated according to the Kaplan-Meier method. The differentiation (myogenic, MD, versus non-myogenic, NMD) was correlated with the outcome using Kaplan-Meier method.

Results: 23 patients with primary PS or LMS of bone were included in the study. Median age was 49 years (range 13-90), male/female 14/9, 18 had localised disease and 5 metastatic disease, 17 received surgery, 14 received adjuvant therapy, 1 received neo-adjuvant chemotherapy and 5 received up-front chemotherapy for advanced disease. All cases were histologically and radiologically reviewed: 17 PS and 6 LMS were identified. All cases were high-grade (FNCLCC grading system). Mutational analysis is currently underway and it will be presented at the meeting. 5-year OS of the whole series was 60% (95% CI; 3,1 – NE) and 5-year DFS was 50% (95% CI; 1,6 – 12,2). Patients with advanced disease are 13: 5-year OS in this subgroup was 38% (95% CI; 2,5 – NE). We identified MD in 11 cases. There were no significant differences between the MD and NMD groups in terms of DFS (logrank p-value=0,6788) and OS (logrank p-value=0,7389).

Conclusions: These primary malignant bone tumours are very rare with poor prognosis after relapse or when radical surgery is not feasible. MD did not predict a worse outcome than NMD in terms of OS and DFS.

Legal entity responsible for the study: Giacomo Giulio Baldi

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1520P Development of a new promising rescue agent for high dose methotrexate (HDMTX) treatment in osteosarcoma: A safety and dose finding study

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Background: HDMTX followed by calcium folinate (CF) rescue is established as part of MAP chemotherapy to manage toxicity during osteosarcoma treatment. A problem with HDTMX is the variability in plasma exposure of both MTX and CF leading to an unpredictable response. A potentially superior rescue agent methylenetetrahydrofolate (Modufolin®), containing the active metabolite of CF, has been evaluated to identify a safe and effective dose for further development.

Methods: This exploratory study performed in Hungary, Poland, Sweden and Czechia involved osteosarcoma patients, 12-40 years, planned for MAP chemotherapy. All patients received one MAP cycle (two HDMTX courses) with standard CF rescue of 15 mg/m^2. Those that completed this MAP cycle successfully according to six defined criteria subsequently received Modufolin® in the following cycle (two HDMTX courses). There were two Modufolin® dose cohorts, 15 mg/m^2 (1) and 7.5 mg/m^2 (2). A Data and Safety Monitoring Board evaluated safety before initiation of the second dose cohort and suggested the dose for further development.

Results: Eight patients 12-17 years were included. Four patients were treated in cohort 1 and four in cohort 2. In cohort 1, no MTX toxicity or delayed elimination with subsequent treatment delay was reported. In cohort 2 one patient reported mucositis grade 3 and failed successful advancement after first course of Modufolin®. In both cohorts and after both types of rescue, there were cases with significantly increased s-creatinine levels.

Conclusions: Modufolin® seems to be a safe and effective rescue agent after HDMTX. The study design however precludes a comparison between Modufolin® and CF, since only patients with successful CF rescue received Modufolin®. The higher dose of 15 mg/m^2 seemed more effective as rescue and was selected for further development.

Clinical trial identification: EudraCT Nr 2013-001280-23

Legal entity responsible for the study: Isofol Medical AB

Funding: Isofol Medical AB

Disclosure: All authors have declared no conflicts of interest.

1521P Role of intraarterial cisplatin and intravenous adriamycin as neoadjuvant and adjuvant chemotherapy in non-metastatic osteosarcoma

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Background: Primary bone sarcomas are rare tumors, comprising approximately 0.2% of all cancers. Because of distant metastasis, cure after surgical treatment alone is uncommon. The development of effective adjuvant or induction chemotherapy regimens has dramatically improved the prognosis and cure rate of 50%–70% and limb salvage in > 90% of cases. For nonmetastatic osteosarcoma(NMO), optimal treatment consists of multiagent neoadjuvant/adjuvant chemotherapy and limb-sparing surgical procedures. The degree of tumor necrosis (TN) after neoadjuvant chemotherapy is one of the most important pronostic indicators. Intraarterial cisplatin and intravenous adriamycin (IC-IA) could achieve a good tumor response.

Methods: Based on achievement of a maximized angiographic response, 106 patients with NMO of the extremities received IC-IA monthly for 3-6 courses between January 1995 and December 2008 followed by limb salvage surgery then adjuvant intravenous (IV) chemotherapy with adriamycin and cisplatin. After resection, if patients had a good response (the extent of TN was ≥ 90%), the same regimen was administered IV every 3 weeks for a total of 6 courses of chemotherapy. Poor responders (tumor necrosis < 90%) were treated with a regimen of high-dose methotrexate with leucovorin rescue (HD-MTX) or ifosfamide, cisplatin, and etoposide (ICE).

Results: Patients received an average of 5 cycles of neoadjuvant IC-IV chemotherapy. 96 patients underwent limb-preservation surgery and 72 had > 90% TN. With an average follow-up of 8years, 60 patients were continuously disease free, 32 died of disease and 14 had no evidence of disease within 5 years after relapse. The 5-year overall survival rate was 70%. No patient developed clinically detectable cardiac toxicity or ototoxicity after adriamycin and cisplatin administration. Febrile neutropenia occurred in few.

Conclusions: This study shows the effectiveness of treating primary NMO of extremities with IC-IA infusion. Advanced bone and soft tissue sarcomas are challenging diseases to treat with an unmet need for effective systemic therapy. Checkpoint inhibitors and Adoptive T cell therapy based immunotherapy could be a new ray of hope in treating bone sarcomas.

Clinical trial identification: Trial Protocol Number IND18745J

Legal entity responsible for the study: Gandhi Medical College and Hamidia Hospital, Bhopal, India

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1522P Biomarkers of malignant cell growth used to assess the risk of osteosarcoma development

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Background: The aim of our study was a comprehensive study of molecular-genetic, pathologic and clinical symptoms in patients with osteosarcoma to enhance the effectiveness of early diagnosis, treatment and prevention of osteosarcomas.

Methods: We studied the immunophenotypic characteristics of tumor cells in 212 patients with osteosarcoma. Results of antibody reactions to Ki-67, bcl-2, p53 (mutant gene) localized in the nuclei and the mitochondrial matrix expressed in % based on the number of stained cells per 100 examined.

Results: Our results revealed that the expression profile of p53 +, bcl-2-, Ki 67+ in 34.9% (74/212) patients with osteosarcoma is considered as poor prognosis, presented as early metastasis, progression of tumor growth and early relapses (15 months), advanced processes (III and IV stage), low grade pathomorposis (1 and 2), the relative duration of lifespan in patients (up to 3 years), it is associated with a low degree of differentiation (G3), an increase in tumor size up to 550 cm3 with chondroblastic type of osteosarcoma. These data should be considered when looking for and isolating the most promising groups for molecular genetic markers that are would be predictive valuable in the clinic for monitoring the treatment of patients with osteosarcoma.

Conclusions: Thus, it is obvious need for clinical medicine in the implementation and expansion of molecular testing for effective decision-making on the appointment of molecular targeted therapy of patients with osteosarcoma. These requires optimization the approach based on consideration of the specifics of the population, the objective conditions related to the presence of intratumoral characteristics. The data reveals a group of patients with osteosarcoma at high risk with unfavorable prognosis at the stage of examination and choose for these kind of patients effective therapy.

Legal entity responsible for the study: National Cancer Research Center of Uzbekistan

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1523P Efficacy of second line treatment with etoposide and ifosfamide in adult patients with advanced Ewing Sarcoma family tumors

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Background: Ewing Sarcoma family tumors (ES) are rare subtypes of sarcomas, and even less common in adult patients. For those not amenable to treatment with curative intent, sequential therapy with multi-agent combinations is the standard of care, usually followed by ifosfamide/etoposide (IE) at the time of progression, largely based on protocols that included pediatric patients. Nevertheless, less is known about the efficacy of this approach for adult patients with ES refractory to first-line therapy.

Methods: We assembled a retrospective cohort of patients aged 18 or older diagnosed with metastatic/inoperable ES refractory to first-line combinations, treated with IE between 2010 and 2016. Patient́s characteristics, tumor variables, treatment outcomes and toxicity data were evaluated. Kaplan-Meier method was used to estimate overall survival and uni/multivariate analysis were carried out to identify factors associated with survival.

Results: Among 18 adult patients, the mean age of diagnosis was 22 years, 73% were male and 84% had an ECOG of 0-1 at commencement of IE. Pelvis and thorax were the most common primary sites. The mean number of cycles of IE was 4. The disease control rate was 27%, with partial responses occurring in 16% of the patients (there were no complete responses). The median OS was 4,8 months (IC 95% 0,7-8,8). Toxicities [3] grade 3 occurred in 61% of the patient, including two treatment-related deaths. The main grade 4 toxicity was febrile neutropenia. Hospitalization were required in 55% of the cases.

Conclusions: IE has limited efficacy and significant toxicity when used in the second-line setting for adult patients with advanced ES, and different approaches should be investigated for these patients.

Legal entity responsible for the study: Instituto do Câncer do Estado de São Paulo

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1524P AG-120, a novel IDH1 targeted molecule, inhibits invasion and migration of chondrosarcoma cells in vitro

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Background: Chondrosarcoma (CS) is the second most frequent primary malignant bone tumor in adults. Surgery is the best treatment option for these patients since most subtypes are resistant to chemotherapy and radiotherapy, thus novel systemic therapies are needed for patients with unresectable tumors. The majority of cases correspond to the conventional central CS histology, were recurrent mutations in isocitrate dehydrogenases *(IDH1/2)* coding genes are found. Therefore, *IDH1* has been reported as a potential therapeutic target and several selective inhibitor molecules, such as AGI-5198 and, more recently, AG-120, have been developed and are currently being evaluated in clinical trials. In this work, we have explored the *in vitro* effects of AG-120 on a central CS cell line, JJ012, which carries a mutation in *IDH1*.

Methods: JJ012 cells were cultured both in monolayer and three-dimensional (3D) spheroids and treated with increasing concentrations of AG-120. *IDH1* mutation in arginine residue R132G was verified by PCR sequencing. Proliferation and cytotoxic screening were done with Sulforhodamine B (SRB) assay. Monolayer invasion and migration assays were performed with FluoroBlok and wound healing assays respectively and 3D experiments were developed using a Matrigel matrix.

Results: R132G mutation of *IDH1* was confirmed by PCR sequencing. Previous reports with AGI-5198 inhibitor show contradictory results regarding their effect on CS cells. In this work, we show how novel molecule AG-120 inhibits both invasion and migration of CS *IDH1* mutated JJ012 cell line in monolayer and 3D cell culture, although it does not affect their proliferation. Minor effects on viability were only detected at high dose (100 μM).

Conclusions: These results support AG-120 as a new possible therapeutic agent for patients with metastatic CS, and further research is needed to understand its action mechanisms in this pathology.

Legal entity responsible for the study: Fundación para la Investigación Biomédica del Hospital Universitario La Paz (FIBHULP)

Funding: Fundación para la Investigación Biomédica del Hospital Universitario La Paz (FIBHULP)

Disclosure: All authors have declared no conflicts of interest.

1525TiP Geriatric assessment of elderly chemotherapy-naïve patients treated with trabectedin for advanced soft tissue sarcomas (STS): The E-TRAB study of the German Interdisciplinary Sarcoma Group (GISG-13)

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Background: More than half of soft tissue sarcoma (STS) patients are diagnosed older than 60 years and prognosis for advanced disease is unfavourable with a median overall survival (OS) of ∼12 months remaining substantially unchanged during the last 20 years. Quality of Life (QoL), especially when collected directly from the patients as Patient Reported Outcome (PRO) measures, has gained increasing interest in cancer care; however, existing data among elderly STS patients are scarce. The rationale of the E-TRAB study is to analyze QoL and PRO data in the elderly population (aged ≥ 60 years) with advanced STS, considered to be unsuited to receive anthracycline-based chemotherapy, and treated with trabectedin as a 1st line therapy.

Trial design: The E-TRAB (GISG-13) study is designed as a non-interventional trial ($n = 110$). Primary endpoints to be evaluated are OS and QoL. It is hypothesized that OS will not be < 10 months in this population. As secondary endpoints a comprehensive geriatric assessment is performed, and whenever feasible captured as PRO, in order to predict for safety parameters consisting of the Instrumental Activities of Daily Living (IADL), the Mini Nutritional Assessment (MNA), the Charlson Comorbidity Index (CCI), the Geriatric Depression Scale (GDS) and Time up & Go. The predictive value of two geriatric screening tools (G8, CARG prediction tool) is investigated with regards to unplanned hospitalizations, grade 4 toxicities and early death within the first six months. The EORTC QLQ-C30 and 18 PRO-CTCAE items are used to evaluate PRO. As translational research the tumour microenvironment is analyzed immunohistochemically using a new multicolor-immunofluorescence-histology technology (OPAL). This trial benefits from a cooperation of sarcoma centers in Austria, Germany and Switzerland under the German Interdisciplinary Sarcoma Group (GISG). The recruitment of patients is ongoing.

Clinical trial identification: NCT03022448

Legal entity responsible for the study: GWT-TUD GmbH

Funding: This investigator-initiated (IIT) study was sponsored by GWT-TUD GmbH, Dresden, Germany, with support from PharmaMar, S.A., Madrid, Spain.

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1526TiP CDK4/6 inhibition in locally advanced/metastatic chordoma (NCT PMO-1601)

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Background: Chordoma is a rare bone tumor with slow growth. The standard treatment is en-bloc excision, but the site of origin of the disease (skull base, sacrum) often prevents complete resection. For these patients, debulking surgery followed by radiation therapy (RT) or high-dose RT alone can be an alternative. However, local relapses and, more rarely, metastatic disease occur, and there is no efficient systemic therapy available. Only very limited responses are seen with chemotherapy or targeted agents (e.g. imatinib, lapatinib). In chordoma cell lines and patient biopsies, the p16 (cyclin-dependent kinase inhibitor 2a, encoded by *CDKN2A*) tumor suppressor is consistently deleted. Experiments with patient-derived chordoma cell lines demonstrated aberrant CDK4/6 activity downstream of p16 loss, which can be efficiently inhibited by the CDK4/6 inhibitor palbociclib, resulting in reduced proliferation and growth of neoplastic cells (von Witzleben et al. Cancer Res 2015;75(18):3823-31).

Trial design: Patients ≥ 18 years of age with locally advanced or metastatic chordoma with at least one measurable tumor lesion, ECOG Performance Status 0-2, adequate organ function, and loss of p16 (as determined by immunohistochemistry) or *CDKN2A* (as determined by genetic analysis) who have no response or have lost response to treatment with a tyrosine kinase inhibitor are eligible. Key exclusion criteria are prior treatment with palbociclib, uncontrolled CNS involvement, cytopenia/s, significant cardiovascular disease including prolongation of the corrected QTc interval >470 ms. Based on previous experience with 125 mg palbociclib once daily for 21 days followed by 7 days of rest in patients with other solid-organ malignancies, this regimen is chosen. Based on a Simon optimal 2-stage design, the disease control rate is the primary endpoint, whereby response is defined as complete response, partial response, or stable disease according to RECIST v1.1 after 6 cycles. For sample size calculation, we estimate a poor response with 10% and a good response with 25% (power, 80%; alpha, 5%), resulting in a first stage of 18 patients and, if 3 or more patients respond, a second stage with 25 additional patients (total, $n = 43$).

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Legal entity responsible for the study: University Hospital Heidelberg

Funding: NCT Heidelberg, Pfizer

Disclosure: R. Schlenk: Research funding: Novartis, Pfizer, Amgen, AtraZeneca, PharmaMar Speakers bureau: Novartis, Pfizer Advisory board: Daiichi Sankyo, Novartis, Pfizer. All other authors have declared no conflicts of interest.

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SCLC

1527O Top-line data from the randomized phase 2 IMPULSE study in small-cell lung cancer (SCLC): Immunotherapeutic maintenance treatment with lefitolimod

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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 the efficacy and safety of lefitolimod in small-cell lung cancer (SCLC).

Methods: IMPULSE is a randomized, international, multicenter, open-label trial to assess the effect of lefitolimod-mediated immune surveillance reactivation on overall survival (OS) in extensive-disease SCLC. 102 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 (control). Upon relapse, patients have received appropriate second-line therapy.

Results: Out of 102 patients, 61 were randomized to the lefitolimod, 41 to the control arm. Distribution of patients to the two arms was balanced regarding patient demographics. Even though in this highly challenging indication the primary endpoint OS of the overall study population was not met, IMPULSE showed positive results in two pre-defined and clinically relevant subgroups: An OS benefit was shown in comparison with the control arm in patients with a low count of activated $CD86^+$ B cells (HR 0.59, 95%CI 0.29-1.21, n = 38 of 88) as well as in patients with reported chronic obstructive pulmonary disease (COPD), (HR 0.54, 95%CI 0.21-1.38, n = 25 of 102). Immunologic parameters confirmed lefitolimod's mode-of-action with a clear activation of $CD169^+$ monocytes and production of IP-10 in response to lefitolimod treatment. Lefitolimod showed a favorable safety profile in this vulnerable population.

Conclusions: The IMPULSE study showed (1) the expected pharmacodynamic response to lefitolimod, (2) positive efficacy signals in two pre-defined and clinically relevant subgroups regarding OS and (3) a favorable safety profile. This data provides significant guidance for defining patient populations most likely to benefit from treatment with lefitolimod.

Clinical trial identification: NCT02200081

Legal entity responsible for the study: Mologen AG

Funding: Mologen AG

Disclosure: M. Schmidt, M. Krikow, E. Wiegert: Employee. All other authors have declared no conflicts of interest.

1528PD Initial results of BMS-986012, a first-in-class fucosyl-GM1 mAb, in combination with nivolumab, in pts with relapsed/refractory (rel/ref) small-cell lung cancer (SCLC)

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Background: Given the burden of comorbidities, lack of curative agents, and high mortality in pts with SCLC, novel treatment options with limited toxicity are needed. BMS-986012 is a first-in-class, fully human mAb with enhanced antibody-dependent cell-mediated cytotoxicity that binds to fucosyl-GM1, a ganglioside highly expressed on SCLC. BMS-986012 monotherapy is well tolerated and has shown evidence of antitumor activity in some pts with rel/ref SCLC in a phase 1/2 study (NCT02247349; Chu et al. Ann Oncol. 2016;27(6 suppl) [abstract 1427PD]). Here we present initial results of BMS-986012 + nivolumab (anti–programmed death-1 mAb) in pts with rel/ref SCLC (NCT02247349).

Methods: Pts with SCLC who relapsed after or were refractory to first-line therapy received BMS-986012 400 or 1000 mg + nivolumab 360 mg IV Q3W. Dose escalation was based on a modified toxicity probability interval design. Primary objectives were safety and tolerability and determination of dose-limiting toxicities (DLT) and maximum tolerated dose. Secondary objectives included pharmacokinetics, antitumor activity, and immunogenicity.

Results: To date, 16 pts received BMS-986012 (400 mg, n = 8; 1000 mg, n = 8) + nivolumab. Demographic and safety data are based on 14 pts treated as of the April 3, 2017 cutoff. Median age was 64 y (range, 49-79 y), ECOG status was 0 (29%) or 1 (71%), and all pts were current (29%) or former (71%) smokers. All pts had prior platinum-based first-line therapy. The most common treatment-related AEs (TRAEs) were generalized pruritus (71%), vulvovaginal pruritus (21%), and dry skin (21%). Only 2 pts, both treated with 1000/360 mg, had G3/4 TRAEs (G3 pruritus with G4 lipase increase; G3 hepatic failure [DLT; led to discontinuation]). As of May 1, 2017, 4 of the 16 pts evaluable for efficacy achieved partial responses (2 unconfirmed). Updated efficacy data as well as data from ongoing biomarker analyses will be presented.

Conclusions: BMS-986012 in combination with nivolumab is well tolerated in pts with rel/ref SCLC, with no evidence of additive toxicity. Promising initial antitumor activity was observed with BMS-986012 + nivolumab in pts with rel/ref SCLC.

Clinical trial identification: NCT02247349

Legal entity responsible for the study: Bristol-Myers Squibb

Funding: Bristol-Myers Squibb

Disclosure: N.B. Leighl: Research funding (institution) - Novartis. Travel/honoraria (unrelated CME) - AstraZenenca, Pfizer, Bristol-Myers Squibb, Merck, Sharpe & Dohme. R.A. Juergens: BMS: advisory board member, honoraria, and grant support; clinical trials funding to my institution (outside of submitted work). P. Basciano, S. Tannenbaum-Dvir, D. Williams, G. Kolaitis: BMS employee; Owner of BMS stock. D. Lathers, K. Urbanska: BMS employee; Ownership of BMS stock. G. Kollia: BMS employee owning company stock. C. Darby: Employee of Mindlance, Inc. and working at Bristol-Myers Squibb under contract. N. Ready: Personal fees from Bristol Myers Squibb, Merck, Celgene, AstraZeneca, and Abbvie outside of submitted work. All other authors have declared no conflicts of interest.

1529PD Activity of lurbinectedin as single agent and in combination in patients with advanced small cell lung cancer (SCLC)

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Background: Lurbinectedin (PM01183, L) is a novel anticancer drug that inhibits activated transcription, induces DNA double-strand breaks generating apoptosis, and modulates tumor microenvironment. Relapsed SCLC still remains an unmet medical need.

Methods: Antitumor activity and safety of Lurbinectedin in SCLC was reviewed in three clinical trials (n = 83 patients): two phase I in combination with doxorubicin (L+DOX; n = 48, two cohorts) or paclitaxel (L+TAX, n = 7), and a phase II single-agent basket trial (n = 28).

Results: Median age was similar in these three studies. CNS was involved in 33% (L+DOX cohort A), 4% (L+DOX cohort B), 29% (L+TAX) and 0% of patients (L alone). Patients with sensitive disease were 52%, 64%, 71% and 71%, respectively. Activity was seen in the three studies (see Table). The most reported toxicity was hematological (G3-4 neutropenia/thrombocytopenia/febrile neutropenia: L+DOX Cohort A 96%/34%/34%; L+DOX Cohort B 89%/11%/14%; L+TAX 86%/0%/14%, and L alone 32%/4%/4%). Non-hematological toxicity was mainly G1-2 and included fatigue, nausea/vomiting, and transaminase increase.

Conclusions: Lurbinectedin shows activity as a single agent and in combination with other agents (DOX and TAX) in relapsed SCLC. Results were remarkable in terms of PFS, DCR and duration of response, especially in platinum-sensitive SCLC. Toxicity mainly consisted of transient myelosuppression, which was manageable with dose reductions and G-CSF use. A randomized Phase III with L+DOX is ongoing (ATLANTIS Study).

Table: 1529PD

Response Evaluable patients	Lurbinectedin+DOX (q3wk)		Lurbinectedin + TAX (q3wk)	Lurbinectedin alone (q3wk)
	Cohort A L 3-5 mg FD D1 + DOX 50 mg/m^2 D1 (n = 21)	Cohort B L 2 mg/m^2 D1 + DOX 40 mg/m^2 D1 (n = 27)	L 2.2 mg/m^2 D1 + TAX 80 mg/m^2 D1 & D8 (n = 7)	L 3.2 mg/m^2 D1 (n = 24)
CR	2 (10%)	1 (4%)	1 (14%)	–
PR	12(57%)	9 (33%)	4 (57%)	6 (25%)
ORR	**14 (67%)**	**10 (37%)**	**5 (71%)**	**6 (25%)**
SD	3 (14%)	9 (33%)	–	12 (50%)
PD	4 (19%)	8 (30%)	2 (29%)	6 (25%)
DCR	**17 (81%)**	**19 (70%)**	**5 (71%)**	**18 (75%)**
DOR (mo)	**4.5**	**3.7**	**2.3**	**6.2+**
PFS (mo) Platinum-sensitive	**5.8**	**5.7**	**4.8**	**3.2+**
PFS (mo) CTFI >30d*	**4.6**	**5.3**	**-**	**-**

D, day; DCR, disease control rate; DOR, duration of response; FD, flat dose; mo, months; q3wk, every 3 weeks; CTFI, chemotherapy free interval.

Clinical trial identification: NCT01970540

Legal entity responsible for the study: PharmaMar SA

Funding: PharmaMar SA

Disclosure: M. Forster: Consulting or advisor or travel and accomodation in Lilly, Pfizer, BI, Novartis Merck, Astrazeneca. E. Calvo: Speakers' Bureau in Novartis and travel or accomodation expenses in Lilly, PsiOxus, Novartis. M.P. Lopez Criado: Relation with Lilly, Bristol, roche, and travel, accomodations with Bristol. J.A. Lopez-Vilarino de Ramos, X.E. Luepke-Estefan: Employee in PharmaMar. C. Kahatt, P. Lardelli, A. Soto-Matos: Employee and Stock in PharmaMar. All other authors have declared no conflicts of interest.

1530PD Results of a randomized, placebo-controlled, phase 2 study of tarextumab (TRXT, anti-Notch2/3) in combination with etoposide and platinum (EP) in patients (pts) with untreated extensive-stage small-cell lung cancer (ED-SCLC)

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Background: Notch signaling is implicated in cancer stem cell biology and is an appealing target in the treatment of SCLC. TRXT, a fully human anti-Notch2/3 antibody, has shown preclinical efficacy in SCLC. A randomized phase 1b/2 study was conducted.

Methods: This was a randomized, placebo-controlled, multi-center study. Pts were randomized 1:1 to platinum (cisplatin 75 mg/m^2 or carboplatin AUC of 5 mg/ml*min on day 1, investigator's choice) + etoposide (EP) 100 mg/m^2 on days 1-3 + TRXT 15 mg/kg on day 1 or EP + placebo (pbo) every 21 days. Chemotherapy was used for 6 cycles, and TRXT/pbo was continued until disease progression. Primary endpoint was progression-free survival (PFS). Secondary endpoints included overall survival (OS), overall response rate (ORR), safety, and PFS/OS in 5 biomarker groups.

Results: 145 pts were enrolled (137 treated). Demographics and baseline pt characteristics were balanced between arms. PFS was similar between the treatment arms (median 5.5 mo in EP+pbo vs 5.5 mo in EP+TRXT, HR = 0.97, p = 0.94). OS was also similar between the treatment arms (median 10.3 mo in EP+pbo vs 9.3 mo in EP+TRXT, HR = 1.01, p = 0.95). ORR was 70.8% in EP+pbo vs 68.6% in EP+TRXT (p = 0.83). There were no statistically significant differences in OS or PFS according to Notch3, Hes1, Hey2, Hey1, or Hes6 gene expression levels. Adverse events (AE) were more common in EP+TRXT; most commonly increased drug-related AEs included diarrhea (33.8/76.8%), thrombocytopenia (17.6/58.0%), decreased appetite (23.5/37.7%), hypokalemia (7.4/33.3%), and vomiting (13.2/31.9%). Most commonly increased grade 3 or higher AEs in the EP+TRXT arm included thrombocytopenia (10.3/40.6%), anemia (20.6/27.5%), pneumonia (4.4/15.9%), diarrhea (0/18.9%), and hypokalemia (4.4/13%). AEs with fatal outcome were more common in EP+TRXT (4.4/8.7%).

Conclusions: Tarextumab in combination with platinum-based therapy did not improve PFS, OS, ORR in previously untreated SCLC. Biomarker analysis failed to establish a predictive marker for TRXT efficacy. Pts treated with TRXT experienced more toxicity. Clinical development of TRXT has been discontinued.

Clinical trial identification: NCT01859741

Legal entity responsible for the study: OncoMed Pharmaceuticals

Funding: OncoMed Pharmaceuticals

Disclosure: S.V. Liu: Consultant: Ariad, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Genentech, Lilly, Pfizer. A. Kapoun, L. Faoro: Employee and stock holder at OncoMed Pharmaceuticals. All other authors have declared no conflicts of interest.

1531PD Clinical outcomes for EGFR-mutant adenocarcinomas (AC) that transform to small cell lung cancer (SCLC)

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Background: About 5-10% of EGFR-mutant lung ACs transform to SCLC at the time of acquired resistance. The clinical course of patients (pts) with this finding is poorly characterized.

Methods: We retrospectively reviewed the records of all 16 pts with EGFR-mutant SCLC that have been seen at our center under an IRB-approved protocol and summarized demographics, disease features, and clinical outcomes.

Results: Among 16 pts, 10 were women. 15 had AC histology at diagnosis; one had *de novo* SCLC with EGFR del19. 11 were never-smokers. All but the *de novo* case received an EGFR tyrosine kinase inhibitor (TKI) prior to transformation (7 had > 1 prior TKI; 6 received a 3rd-gen TKI) and 14/15 were on a TKI when the SCLC was noted. Median time from diagnosis to SCLC was 29.6 mo (95% CI 10.8-38.1). 15/16 of the SCLC tumors were genotyped; all kept their founder EGFR mutation and none had T790M, including 5 pts with prior T790M-positivity. Not all samples were assessed for genotype by the same assay, though recurrent mutations observed in at least 25% of cases were TP53, PIK3CA and RB1 (full genetic data will be shown at meeting). The most common therapy given directly after SCLC diagnosis was platinum-etoposide (n = 9); all SCLC treatment lines considered, platinum-etoposide had a clinical response rate of 72% (8/11) and progression-free survival of 4.6 mo (95% CI 2.0-5.5). Seven pts also had a taxane at some point after the diagnosis of SCLC, and 4/7 (57%) responded. Median overall survival (mOS) from initial cancer diagnosis was 38.2 mo (95% CI 24.5-43.9) and mOS from time of SCLC diagnosis was 12.4 mo (95% CI 4.0-16.6).

Conclusions: EGFR-mutant AC that transforms to SCLC uniformly maintains its founder EGFR mutation and is mutually exclusive with T790M (though both can be observed sequentially). In our cohort, the median time from initial lung cancer diagnosis to transformation was 2.5 years. The mOS of 12.4 mo following diagnosis of SCLC is

similar to that seen among pts with non-EGFR-mutant SCLC. Likewise, responses to platinum-etoposide were frequent, but transient. 4 pts also responded to a taxane. Interestingly, mOS from diagnosis was similar to expected mOS for pts that never transform to SCLC at 38.2 mo. Further investigation is needed to better elucidate optimal strategies for this group.

Legal entity responsible for the study: Lecia V Sequist

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1532P The role of thoracic radiotherapy on peripheral lymphocyte subsets in patients with limited-stage small cell lung cancer

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Background: Over the past decades, there has been a lack of significant breakthroughs in small cell lung cancer therapy, the current standard care is still concurrent chemoradiation. Recently, immune checkpoint inhibitors in anti-tumor clinical application has achieved remarkable results. There is evidence suggest that radiation and chemotherapy can alter the immune microenvironment, many clinical trials combing radiation or chemotherapy with checkpoint inhibitors are underway. But how chemotherapy or radiotherapy affects any existing anti-tumor immune response and how that response is changed following clinical treatment are still not elucidated fully. In this study, we investigated the changes of immune subsets in patients with LS-SCLC.

Methods: Blood samples were obtained from 48 patients before and after radiotherapy and 31 patients before and after induction chemotherapy. PBMCs were purified using standard Ficoll density gradient centrifugation. The percentage of circulating lymphocyte subsets were measured by flow cytometry. Patient data include clinical characteristics, disease prognostic information, survival information etc. The SPSS 22.0 software was used for the data analysis.

Results: Among the 31 patients, most values of T-lymphocyte subsets showed no statistically significant difference before and after induction chemotherapy. Among the 48 patients, remarkable elevation of CD3+, CD8+ T cells were noticed, CD4+, CD56+, CD4+CD45RA+ cells and CD4+/CD8+ ratio were significantly decreased after radiotherapy. Then we further analyzed the changes of lymphocyte subsets in 17 patients before and after induction chemotherapy as well as radiotherapy, which further confirmed the changes of immune subsets caused by radiotherapy but not induction chemotherapy.

Conclusions: This study suggest that thoracic radiotherapy but not induction chemotherapy has an immunomodulatory effect on LS-SCLC patients, which provides new insights relevant for designing more optimal combination of immunotherapy in such cohort, especially for the appropriate time and sequence of immunotherapy, radiotherapy and chemotherapy.

Legal entity responsible for the study: Yamei Chen

Funding: National Natural Science Foundation of China

Disclosure: All authors have declared no conflicts of interest.

1534P Antidepressants simulate enriched environment enhance platinum chemosensitivity of small cell lung cancer

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Background: Small cell lung cancer (SCLC) is one of the most lethal malignancies with rapid chemoresistance. Numerous studies have been devoted to reversing chemoresistance. However, it is still far from successful with a clear way to reverse the effect of chemoresistance. Based on our previous study, enriched environment (EE) has a clear effect on improving the mental state of mice and can reduce chemotherapy resistance caused by platinum regimens. In this study we investigated the complex links between benign mental stress (EE) and chemosensitivity of SCLC, and use anti-depressants to improve the mental state of mice to observe its impact on chemosensitivity to platinum regimens, and the underlying mechanism was explored.

Methods: The mental state of mice was comprehensive evaluation by behavior tests include: elevated plus maze (EPM), open field experiment (OF), forced swimming (FS). Then, the mice were transplanted subcutaneously and treated with cisplatin, carboplatin and oxaliplatin. Tumor growth and the results of behavior test were analyzed. The tumor was analyzed by gene expression profiling and the differential genes were screened. The expression level of differential genes were examed by real-time PCR, and verified by western bolt and immunohistochemistry, respectively. And then we examined the effects of antidepression drugs inducing chemoresistance in NCI-H69 cell, and ABCG2 blocker was used for chemosensitivity verification in vivo and in vitro.

Results: EE significantly increased the time of movement of the in the EPM (35.24 sec V.S. 16.78 sec, $P < 0.01$), increased the center area time in OF test (54.25 sec V.S. 35.24 sec, $P < 0.05$), significantly increased the struggling time in the FS test (46.02 sec V.S. 25.81 sec, $P < 0.01$). For antidepressants, its can also significantly improve the state of depression of mice, improve the behavior results, but can not achieve the effect of EE (EPM: 30.25 sec V.S. 35.24 sec, OF: 49.84 sec V.S. 54.25 sec, FS: 37.28 V.S. 46.02 sec). For platinum chemosensitivity test, the antidepressant drugs (Diazepam, Quetiapine and Clomipramine) without direct inhibition to NCI-H69 cells. Antidepressants and EE have significantly increased the sensitivity of chemotherapy in mice, but antidepressants can not achieve the inhibitory effect of EE. We detected the serum of mice and found that the serum BDNF levels significantly decreased in EE mice. Similarly, antidepressants also significantly reduced serum BDNF levels in mice. Gene expression profiles showed that a variety of genes were downregulated in the tumor tissue of EE and antidepressants mice, mainly in ABC transporters and drug metabolic pathways. The expression level of ABCB1, ABCC2, ABCG2, ABCC9, PPARa, DPYD, GST-P1 and GSTM1 in NSCLC sample were examedby real-time PCR, and verified by western bolt and immunohistochemistry, respectively. ABCG2 expression in tumor of EE and antidepressants mice were even 3-fold higher than control ($P < 0.001$), and the same results were obtained by WB and IHC verification. Nicardipine blocks ABCG2 expression can restore chemosensitivity to platinum based drugs ($P < 0.001$).

Conclusions: Antidepressants can partially mimic the chemotherapeutic effect of EE and we confirm that the mechanism is partially achieved by increasing BDNF and reducing the expression of ABCG2.

Legal entity responsible for the study: Henan Cancer Hospital

Funding: Research Foundation of Henan Cancer Hospital (nos. 201511004 to Yufeng Wu)

Disclosure: All authors have declared no conflicts of interest.

1535TiP KEYNOTE-604: Phase 3 trial of pembrolizumab plus etoposide/platinum (EP) for first-line treatment of extensive stage small-cell lung cancer (ES-SCLC)

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Background: Therapeutic options for SCLC remain limited, with EP as the standard first-line chemotherapy regimen. However, patients (pts) with ES-SCLC experience high relapse rates within months after initial therapy. Pembrolizumab, a humanized monoclonal antibody against PD-1, has shown antitumor activity as monotherapy in heavily pretreated pts with PD-L1–positive SCLC in the phase 1b KEYNOTE-028 study. KEYNOTE-604 (ClinicalTrials.gov, NCT03066778) evaluates EP plus either pembrolizumab or placebo (pbo) as first-line therapy for ES-SCLC.

Trial design: In this international, double-blind, phase 3 trial, adults with newly diagnosed ES-SCLC, ECOG PS ≤ 1, and no previous systemic therapy for SCLC are randomized 1:1 to receive either EP plus a 200-mg fixed dose of pembrolizumab intravenously (IV) once every 3 weeks (Q3W) or EP plus pbo IV Q3W. Randomization is stratified by the chosen platinum therapy (carboplatin vs cisplatin), ECOG PS (0 vs 1), and baseline lactate dehydrogenase concentration ($\leq$ upper limit of normal [ULN] vs $>$ ULN). Study treatment includes a total of 4 cycles of EP and 2 y of pembrolizumab/pbo and continues until documented PD, intolerable toxicity, or withdrawal of consent. Pts with a response after 4 cycles of EP plus pbo or pembrolizumab may receive prophylactic cranial irradiation. Pts who complete 2 y of pembrolizumab treatment or stop pembrolizumab for reasons other than PD/intolerability, but subsequently have documented PD, may receive an additional 1 y of pembrolizumab. Tumor response is assessed every 6 wk for 48 wk, and every 9 wk thereafter by RECIST version 1.1 by blinded independent central review. AEs occurring during treatment and 30 d thereafter (90 d for serious AEs) are graded per Common Terminology Criteria for Adverse Events, version 4.0. Primary endpoints are PFS and OS. Secondary endpoints are ORR, duration of response, safety, and patient-reported outcomes. Enrollment is ongoing with a planned enrollment of approximately 430 pts.

Clinical trial identification: NCT03066778; EudraCT Number: 2016-004309-15

Legal entity responsible for the study: Merck & Co., Inc., Kenilworth, NJ, USA

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Disclosure: C.M. Rudin: Advisory board member: Abbvie, Araxes, BMS, Celgene, G1 Therapeutics, Harpoon, Novartis. L. Shen, M.C. Pietanza: Employee of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ USA.

1536TiP An open-label study on safety and tolerability of rovalpituzumab tesirine in Japanese patients with advanced, recurrent small cell lung cancer

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Background: Small cell lung cancer (SCLC) is a chemoresponsive malignancy with high response rates in early lines of therapy, but will inevitably recur. For patients (pts) with progressive SCLC following treatment with at least two prior therapies, standard treatment has not been established. Rovalpituzumab tesirine (Rova-T^{TM}) is an antibody-drug conjugate that targets Delta-like protein 3 (DLL3), an atypical Notch receptor family ligand and a marker specific for tumor-initiating cells in SCLC and other neuroendocrine cancers. Rova-T is comprised of a humanized DLL3-specific IgG1 monoclonal antibody tethered to a toxic DNA cross-linking agent by a cleavable linker. Rova-T binds DLL3 on target-expressing cells, is internalized, and the toxin released to induce cell death. A Phase 1 study of Rova-T in SCLC demonstrated robust antitumor activity in DLL3-high pts and a manageable safety profile[1]. The safety, tolerability, pharmacokinetics (PK), and pharmacodynamics of Rova-T has not been evaluated in Japanese SCLC pts, thus a study of Rova-T in this population is warranted.

Trial design: This is a Phase 1, multicenter, Japanese, open-label dose escalation study (NCT03086239). Primary objective: to assess safety and tolerability of Rova-T in Japanese pts with advanced, recurrent SCLC. Secondary objectives: to explore antitumor activity of Rova-T; to study PK and pharmacodynamics of Rova-T. Pt eligibility: histologically or cytologically confirmed advanced, recurrent SCLC with measurable disease and documented disease progression after at least 2 prior systemic regimens, including at least 1 platinum-based regimen; ECOG 0-1; no prior exposure to a pyrrolobenzodiazepine-based drug. A standard 3 + 3 dose escalation will be used with $\leq$ 18 pts enrolled (6/dose level x 3 levels) and $\leq$ 60 pts if expansion cohorts are executed (20/dose level x 3 levels). Pts will receive Rova-T 0.2, 0.3, or 0.4 mg/kg intravenously on Day 1 of each 6-week cycle x 2 doses and dexamethasone 8 mg orally twice daily on Day -1, Day 1, and Day 2 of each 6-week cycle. Dose escalation will proceed until a single maximum tolerated dose (MTD) is determined (not to exceed 0.4 mg/kg). 1. Rudin et al., Lancet Oncol, 2016.

Clinical trial identification: NCT03086239

Legal entity responsible for the study: AbbVie Stemcentrx

Funding: AbbVie Stemcentrx

Disclosure: I. Okamoto, H. Udagawa, S. Kanda, M. Takeda, H. Akamatsu: Serves as an investigator for Abbvie Stemcentrx. T.H. Han, I. Lakatos, F. Zhang, C. Scripture: Employee of AbbVie Stemcentrx and may own AbbVie stock. S. Okubo: Employee of AbbVie and may own AbbVie stock. All other authors have declared no conflicts of interest.

1537TiP A phase 3 trial of rovalpituzumab tesirine vs topotecan in patients with advanced small cell lung cancer following frontline platinum-based chemotherapy

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Background: Small cell lung cancer (SCLC) represents ~15% of lung cancers. Patients (pts) are staged with limited or extensive stage disease (ES). ES standard therapy consists of a platinum-based therapy + a second agent (etoposide). Initial response rates are high but not durable. Treatment for relapsed pts is limited, but includes topotecan. However, efficacy of topotecan is suboptimal and there is a high unmet need in this population. Delta-like protein 3 (DLL3) is an atypical Notch receptor family ligand identified as a target in SCLC and neuroendocrine carcinomas (NECs). DLL3 is highly expressed in SCLC and NECs but not normal tissue. Rovalpituzumab tesirine (Rova-T^{TM}) is an antibody-drug conjugate composed of a DLL3-targeting IgG1 monoclonal antibody tethered to a toxic DNA crosslinker. Rova-T has antitumor activity in relapsed ES SCLC pts, and was well-tolerated[1]. Thus, we are investigating Rova-T vs topotecan as a 2nd line therapy in advanced SCLC.

Trial design: This is a Phase 3, randomized, open-label, multicenter study (NCT03061812) to assess efficacy, safety, and tolerability of Rova-T vs topotecan. Approximately 411 pts will be enrolled and randomized 2:1 between 2 arms. Arm A regimen: 0.3 mg/kg Rova-T intravenous (IV) on Day 1 + 8 mg dexamethasone orally, twice daily on Day -1, 1 and 2 of a 42-day cycle; administered for 2 cycles with up to 2 additional cycles permitted. Arm B: 1.5 mg/m^2 topotecan (or per local label) IV on Days 1-5 of each 21-day cycle; administered until disease progression. Pt eligibility: $\geq$ 18 years; confirmed, advanced/metastatic SCLC with first disease progression following frontline standard therapy; DLL3-high tumor expression; ECOG 0-1; no prior exposure to a pyrrolobenzodiazepine-based drug or topotecan, irinotecan, or other topoisomerase I inhibitor. Primary objectives: to determine if Rova-T improves objective response rate and overall survival vs topotecan. Secondary objectives: to assess if Rova-T improves progression-free survival vs topotecan; to compare duration of objective response between arms; and to assess effect on patient-reported outcomes. 1. Rudin et al., Lancet Oncol, 2016.

Clinical trial identification: NCT03061812

Legal entity responsible for the study: AbbVie Inc.

Funding: AbbVie Inc.

Disclosure: P. Komarnitsky, H-J. Lee, M. Shah, S. Wong, S. Gulbranson, J. Dziubinski, L. Caffrey, P. Tanwani, M. Motwani, F. Zhang: Employee of AbbVie and may own stock.

1538TiP A phase 1/2 study on safety of rovalpituzumab tesirine in combination with nivolumab or nivolumab + ipilimumab in small cell lung cancer

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Background: Small cell lung cancer (SCLC) is an unmet medical need, representing ~15% of lung cancer diagnosed/year. Two-thirds of patients (pts) are diagnosed with extensive stage (ES) SCLC with a 2-year survival rate of 5%. Delta-like protein 3 (DLL3), an atypical Notch receptor family ligand, is highly expressed in SCLC and other neuroendocrine tumors with little to no expression in normal tissue. Rovalpituzumab tesirine (Rova-T^{TM}) is an antibody-drug conjugate composed of a humanized DLL3-specific IgG1 monoclonal antibody tethered to a toxic DNA cross-linking agent. A Phase 1 study of Rova-T in SCLC pts showed encouraging progression-free and overall survival and a manageable safety profile[1]. Studies show that nivolumab (nivo, anti-PD-1 antibody) +/- ipilimumab (ipi, anti-CTLA-4 antibody) has antitumor activity and is well-tolerated in 2nd line SCLC. Given the complementary mechanisms of action and non-overlapping toxicities, futher study is warranted to evaluate if a combination of Rova-T and nivo, or all 3 agents leads to more pts with long-term responses and prolonged survival.

Trial design: This Phase 1/2 study (NCT03026166) will enroll ~90 pts in 3 cohorts. Each cohort will receive Rova-T 0.3 mg/kg IV on Day 1 of the 1st and 3rd 3-week cycle in combination with: nivo 360 mg/kg IV q3wk x 2 cycles (cohort 1) or nivo 1 mg/kg q3wk + ipi 1 mg/kg (cohort 2) or 3mg/kg (cohort 3) IV q3wk x 4 cycles. Maintenance nivo will be administered in all cohorts at 480 mg IV q4wk. The dose limiting toxicity (DLT) evaluation period is 12 weeks. Pt eligibility: $\geq$ 18 years; histologically or cytologically confirmed 2nd line or later ES SCLC; confirmed DLL3-positive status based on immunohistochemistry of baseline tumor tissue (for DLT evaluable pts); ECOG 0-1; no autoimmune disease; no prior exposure to immuno-oncology or pyrrolobenzodiazepine-based drugs. Primary and secondary objectives: assess safety and efficacy of Rova-T in combination with nivo or nivo + ipi. Exploratory objectives: assess expression of DLL3 and PD-L1 and their relationship to clinical outcome, pharmacokinetics, incidence of neutralizing antibodies, and effects on pharmacodynamic biomarkers. 1. Rudin et al., Lancet Oncol, 2016.

Clinical trial identification: NCT03026166

Legal entity responsible for the study: AbbVie Stemcentrx

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Disclosure: C. Scripture, I. Lakatos, K. Boynton, S. Lally, T.H. Han, S.L. Peng, S.J. Dylla: Employee of AbbVie Stemcentrx and may own stock. G. Selvaggi: Employee of Bristol-Myers Squibb.

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SUPPORTIVE CARE

1539O Pre-chemotherapy nutritional status and chemotherapy response: An observational study

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Background: Cancer patients undergoing chemotherapy suffer from nausea, vomiting, low blood counts and electrolyte disturbances that impose stress on the nutritional needs of cancer patients. Nutritional status has been shown to reflect not just the patient's general condition but also to predict patient survival. In this study, we evaluate the predictive effects of pre-chemotherapy nutritional status in patients with solid malignancies on chemotherapy response and quality of life.

Methods: Two hundred adult patients with localized solid malignancies (Except GI and Brain malignancies) undergoing Neoadjuvant/adjuvant chemotherapy were analyzed for their nutritional status before the therapy. Nutritional status was assessed using Subjective Global assessment (SGA), Nutritional risk index (NRI), Body mass Index (BMI), Platelet lymphocyte ratio (PLR), neutrophil-lymphocyte ratio (NLR), and Albumin-globulin ratio (AGR) prior to their chemotherapy treatment. Patients were also assessed for Hand grip strength, Quality of life using Functional assessment of Chronic illness Therapy (FACIT) and EUROQol C30 and radiological response using RECIST criteria following chemotherapy.

Results: Mean age of study population was 51.65 $\pm$ 10.1years. Multivariate regression analysis was done on Chemotherapy outcomes such as Response criteria, FACIT scores, Quality of life scores and handgrip strength using, SGA, NRI, NLR, BMI and Albumin/Globulin ratio as predictors. SGA score emerged as a significant primary predictor for hand grip strength (β=-7.3, $p < 0.001$) followed by BMI ($\beta = 1.3$, $p < 0.001$) and NRI (β=-0.73, $p < 0.001$). SGA emerged a significant primary predictor for FACIT score ($\beta = 16.1$, $p < 0.001$) followed by NLR (β=- 0.43, $p = 0.008$). SGA emerged as a significant primary predictor for physical activity ($\beta = 1.73$, $p < 0.001$) followed by BMI (β=-0.19). SGA emerged as a significant predictor of quality of life score (β=-3.13, $p < 0.001$). Multinomial logistic regression for a complete response to RECIST criteria showed lower NLR to be a significant predictor ($\beta = 0.90$, $p = 0.04$).

Conclusions: The results suggest that pre-chemotherapy nutritional status and NLR influence the functional quality of life, strength and chemotherapy response in patients with solid malignancies.

Legal entity responsible for the study: Raghavendra Rao M

Funding: HCG Foundation

Disclosure: All authors have declared no conflicts of interest.

1540O Fosaprepitant reduces the impact of nausea on daily function during five weeks of chemo-radiotherapy: A sub-study of the GAND-emesis trial

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Background: The GAND-emesis trial, a multinational, randomised, double-blind, placebo-controlled phase III trial, in women with cervical cancer receiving fractionated radiotherapy and weekly cisplatin 40 mg/m^2, demonstrated an increase of 17% in the proportion of patients completing five weeks of treatment without vomiting when fosaprepitant (FOS) was added to palonosetron (PAL) and dexamethasone (DEX) (Ruhlmann et al, Lancet Oncol, 2016). As a secondary endpoint we investigated whether there was any difference in impairment of daily functional life between groups as a result of nausea or vomiting.

Methods: The validated Functional Living Index – Emesis (FLIE) questionnaire consists of 18-items to measure the impact of nausea (9 items domain) and vomiting (9 items domain) on daily functional life. The FLIE-questionnaire was completed at baseline and again at end of study (EoS). The scores for each domain and the total score were calculated according to the FLIE Manual. Domain scores $\geq$ 54 and total score $\geq$ 108 indicate no or minimal impact on daily life. The Kruskal-Wallis H test was used to test the difference between groups.

Results: Two hundred and thirty-four patients from four countries were randomised and received study medication. Nine patients were excluded due to invalid questionnaires. Included were 115 patients receiving FOS and 110 patients receiving placebo (PLA). The point scores at baseline were similar across groups (FOS vs PLA); nausea domain: 59.9 vs 60.3 ($p = 0.31$); vomiting domain: 61.9 vs 62.1 ($p = 0.16$); and total score: 121.8 vs 122.4 (0.37). At EoS, a statistically significant difference was demonstrated for the point scores for the nausea domain and the total score (FOS vs PLA); nausea domain: 54.9 vs 53 ($p = 0.02$); vomiting domain: 61.4 vs 60.9 ($p = 0.10$); and total score: 116.3 vs 113.9 ($p = 0.01$).

Conclusions: This is the first study to investigate safety, efficacy, and impact on daily function of a neurokinin-1 receptor antagonist during the entire course of concomitant chemo-radiotherapy. The addition of FOS to PAL and DEX not only improved emetic control but also gave a clinically and statistically significant reduction of the impact of nausea on patients' daily functional life.

Clinical trial identification: EudraCT number: 2009-014691-21. ClinicalTrials.gov: NCT 01074697.

Legal entity responsible for the study: Sponsors delegate and coordinating investigator Christina H. Ruhlmann/for sponsor Prof. Jørn Herrstedt, Odense University Hospital

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Disclosure: F. Hilpert: Grants from Riemser Pharma during the conduct of the study. P. Feyer: Grants from Riemser Pharma during the conduct of the study; advisory consultant for MSD, outside the submitted work. D. Keefe: Grants from Helsinn, other from Merck, outside the submitted work J. Herrstedt: Unrestricted grant from Helsinn Healthcare, and an unrestricted grant from SOBI, during the conduct of the study; personal fees from Tesaro outside the submitted work. All other authors have declared no conflicts of interest.

1542PD Anticipative approach to improve safety: An innovative daily hospital organisation

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Background: The PROCHE [Programme for optimisation of the chemotherapy network] initiative is an innovative oncology-monitoring program designed to reduce patient waiting time and chemotherapy wastage, ultimately improving patient care. A nurse calls patients 48 hours before anticancer treatment at the daily hospital to anticipate chemotherapy preparation.

Methods: Primary objective was to evaluate the incidence of different symptoms reported by grade (NCI-CTC AE: from 0 to 4) prospectively collected from 2008 to 2016. Secondary objective compared the 2009-2016 patients to the control cohort (2008 period) quantified using Mantel-Haenszel khi^2 and exact *p-values.*

Results: From January 2009 to December 2016, 3012 patients were enrolled in the program, representing 36 803 questionnaires completed over the whole period. Main adverse events (AE) were collected and compared to the control cohorts (2008, n = 513),

Table: 1542PD

Adverse Event	2008 (%)	2009-2016 (%)	p-value
Fatigue	82.4	62.01	<0.0001
Pain	49.69	28.31	<0.0001
Neuropathy	35.77	39.06	0.0784
Nausea	29.92	11.38	<0.0001
Vomiting	8.03	2.26	<0.0001
Infection	7.91	3.48	<0.0001
diarrhea	13.56	7.88	<0.0001
Constipation	34.42	19.28	<0.0001
Dry Skin	38.72	25.21	<0.0001
Hand Foot Syndrome	15.28	2.47	<0.0001
Mucositis	15.54	9.87	<0.0001

resulting in a significant decrease in majority of topics. Global incidence comparison is presented in table 1, with the p-value according to khi2 test. Details of severity levels scores using NCI CTC-AE V4.0, will be reported at ESMO meeting. For some of the toxicities, severe or life threatening toxicities (grades 3-4) were higher in the PROCHE cohort, while global incidence decreased.

Conclusions: The PROCHE initiative resulted in adverse events decrease and improved patient quality of care and improved hospital as well as pharmacy efficacy.

Legal entity responsible for the study: Florian Scotté

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1544PD Development of an online drug-drug interaction resource to support prescribing of oncolytics

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Background: Patients treated for cancer are at high risk of drug-drug interactions (DDI), which affects nearly 60% of patients on therapy. We developed a freely available DDI resource (www.cancer-druginteractions.org) to support anti-cancer drug prescribing, based on successful implementation for HIV (www.hiv-druginteractions.org) and hepatitis (www.hep-druginteractions.org) treatments.

Methods: A review of literature and registration documents was performed to evaluate the available evidence for potential DDIs of several oncolytics. Decision trees based on the FDA guideline on DDI studies were used to assess clinical relevance of DDIs. Comedications that are frequently used by cancer patients were selected. Interaction potential of drug combinations was classified using a straightforward 'traffic light' classification and quality of evidence was classified using the GRADE system. Advice on management of the interaction was included where appropriate. All records were reviewed by an expert panel of clinical pharmacists/pharmacologists.

Results: Thus far, twelve targeted oncolytics for the indications renal cell, hepatocellular and ovarian carcinoma, gastrointestinal stromal tumors, neuroendocrine tumors and sarcoma have been reviewed. Potential DDIs between oncolytics and > 450 comedications have been classified (Table). Tyrosine kinase inhibitors (TKI) show potential interactions which require action of prescribers in more than 20% of reviewed drug combinations. Monoclonal antibodies (MoAB) show clinically relevant DDIs in only 0.7% of reviewed drug combinations.

Table: 1544PD Overview of evaluated DDIsc

Drug class	TKI	MoAB
Number of comedications screened for interaction potential (mean)	458	478
Interaction classi˚cation 'traf˚c light' (%)		
Green: No clinically significant interaction	64.8	80.6
Yellow: Interaction of weak/moderate intensity; no a priori dosage adjustment required	14.4	18.7
Amber: Potential interaction which may require dosage adjustment or close monitoring	17.5	0.6
Red: Do not co-administer	3.3	0.1

Conclusions: The DDI checker currently includes comprehensive and ready-to-use advices for DDIs with oncolytics for six indications (these are due to be expanded in the coming months). The freely available, independently developed website with 'traffic light' classification will facilitate health care professionals' and patients' awareness of potential DDIs between oncolytics and frequently used comedications.

Legal entity responsible for the study: Radboud University Medical Center

Funding: Abbvie, Astellas, AstraZeneca, Boehringer Ingelheim, Gilead, Pfizer

Disclosure: K. McAllister, S.H. Khoo: Educational grant from Abbvie and Gilead to perform this project. N.P. Van Erp: Educational grant from Astellas, AstraZeneca, Boehringer Ingelheim, Gilead and Pfizer to perform this project. All other authors have declared no conflicts of interest.

1545PD The effect of cannabis use on tumor response to nivolumab in patients with advanced malignancies

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Background: In recent years, immunotherapy, which enhances the immune system's response to tumors, has come into clinical use. At the same time, the use of cannabis, which has potential immune-suppressive effects, is increasing in oncology patients, mainly for palliative indications. A large number of patients is being treated with these two modalities and interaction is possible. The aim of this study was to evaluate the influence of cannabis use during immunotherapy treatment on response rate (RR), progression-free survival (PFS) and overall survival (OS).

Methods: In this retrospective, observational study, data was collected from the files of patients treated with Nivolumab in the years 2015-2016 at Rambam Health Care Campus in Haifa, Israel. Nivolumab was given to 140 patients (89 Nivolumab alone, 51 Nivolumab plus cannabis) with advanced melanoma, non-small-cell lung cancer, and renal clear cell carcinoma. The groups were homogenous regarding demographic and disease characteristics. A comparison of patients treated with Nivolumab plus cannabis to Nivolumab alone was made.

Results: In a multi-variant model, cannabis was the only significant factor which reduced RR to immunotherapy (37.5% RR in Nivolumab alone compared to 15.9% in the Nivolumab plus cannabis group ($p = 0.016$, OR = 3.13, CI95% 1.24-8.13). Cannabis use was not a significant factor for PFS or OS. Factors affecting PFS were smoking (adj HR = 2.41), brain metastases (adj HR = 2.04), and response to therapy (adj HR = 4.89). Factors that reduced OS were smoking (adj HR = 2.41), brain metastases (adj HR = 2.83), hypertension (adj HR = 2.28), low performance status and disease progression (adj HR = 2.83).

Conclusions: In this retrospective analysis, the use of cannabis in combination with immunotherapy decreased RR to treatment, without affecting PFS or OS. This information can be critical for a large group of patients, and requires caution when starting immunotherapy. Considering the limitations of the study, further prospective clinical study is needed to investigate possible interaction.

Legal entity responsible for the study: Local Helsinki Committee (IRB)

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1546PD Impact of sarcopenia on dose limiting toxicities in metastatic colorectal cancer patients (mCRC pts) receiving palliative systemic treatment

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Background: Evidence is increasing that severe skeletal muscle (SM) loss (sarcopenia) is associated with reduced overall survival (OS) in mCRC pts. We recently found, using data of the randomized phase 3 CAIRO3 study (*Lancet, 2015*), that SM loss was related to shorter time to progression during first line maintenance treatment (Tx) with capecitabine+bevacizumab (CAP-B) or observation. Subsequently, SM loss during more intensive reinduction Tx by adding oxaliplatin (CAPOX-B) was associated to shorter overall survival (*ASCO, 2017*). As a potential risk factor for reduced survival we explored whether sarcopenia was associated with dose reductions at start of CAPOX-B reinduction Tx and dose limiting toxicities (DLT) during CAPOX-B reinduction Tx.

Methods: Here, CAIRO3 pts were included who received CAPOX-B reinduction Tx. DLT were defined as any dose delay, reduction, or discontinuation of systemic treatment because of reported CTCAE (v3.0) toxicities at start or during Tx. Poisson regression models adjusted for relevant confounders were used to study the association between sarcopenia and DLT.

Results: A total of 254 pts received CAPOX-B reinduction Tx. 39% of pts were sarcopenic and compared to normal SM pts we found no statistically significant differences in age and sex (sarcopenic vs normal SM: mean age 63.6±9.1 vs 61.9±8.5 yrs, p=.20 and 39% vs 31% females p=.31). BMI was significantly lower in sarcopenic pts, but pts were on average still overweight (25.9±3.8 vs 27.2±3.8 p=.01). Overall, 67% experienced ≥1 DLT. At start of CAPOX-B, 25% had already received a dose reduction and the risk of dose reduction at start was significantly higher for sarcopenic compared to

normal SM pts (RR 1.8 95%CI 1.08-2.90). Despite more frequent dose reductions at start, sarcopenic pts did not have a significantly lower risk of DLT during CAPOX-B Tx (RR sarcopenic vs normal SM pts 0.86 95% CI 0.46-1.45).

Conclusions: Sarcopenia was significantly associated with dose reductions at start of CAPOX-B reinduction Tx, and not with DLT during CAPOX-B reinduction Tx. Possible explanations for dose reductions at start might be more frequent toxicities during previous Tx including neuropathy.

Clinical trial identification: NCT00442631

Legal entity responsible for the study: Dutch Colorectal Cancer Group (DCCG)

Funding: Province of Utrecht, The Netherlands

Disclosure: B. Dorresteijn, M. Jourdan: Employee of Nutricia Research All other authors have declared no conflicts of interest.

1547PD Phase 3 safety evaluation of an intravenous formulation of NEPA, a novel fixed antiemetic combination of fosnetupitant and palonosetron

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Background: NEPA, an oral fixed combination of the highly selective NK_1RA netupitant (300 mg) and clinically/pharmacologically distinct 5-HT_3RA palonosetron (PALO, 0.50 mg) is the first fixed-dose antiemetic combination to have been approved. A single oral NEPA capsule plus dexamethasone (DEX) given prior to AC and non-AC highly emetogenic chemotherapy (HEC) showed superior prevention of chemotherapy-induced nausea and vomiting (CINV) over PALO plus DEX for 5 days post-chemotherapy; the safety of NEPA was also well-established in the Phase 2/3 clinical program in 1442 NEPA-treated patients. An intravenous formulation of the NEPA combination (fosnetupitant 260 mg/PALO 0.25 mg) is under development.

Methods: This randomized, multinational, double-blind, stratified (by gender and country) Phase 3 study in chemotherapy-naïve patients with solid tumors was designed to assess the safety of a single 30-minute infusion of IV NEPA prior to initial and repeated cycles of HEC. Patients received either IV NEPA or oral NEPA, both with oral DEX on days 1-4. Safety was assessed primarily by treatment-emergent adverse events (TEAEs) and also by laboratory tests, vital signs and ECGs.

Results: 404 patients were included in the safety population (203 IV NEPA, 201 oral NEPA) for a total of 1312 exposures. Overall, 53% of patients were male, 99% were white and the mean age was 60 years. Cisplatin was the most frequent HEC (96% of patients) and lung cancer was most common (55% of patients). The TEAE profiles for cycle 1 (**Table**) and in all cycles were similar for the two treatment groups. There was no increased incidence of TEAEs in subsequent cycles. No clinically relevant changes in QTc and no cardiac safety concerns were seen. No infusion site reactions related to IV NEPA occurred.

Table: 1547PD

Cycle 1 n (%) patients with	IV NEPA (N = 203)	Oral NEPA (N = 201)
At least one treatment emergent adverse event (TEAE)	120 (59.1%)	135 (67.2%)
Severe TEAEs	50 (24.6%)	51 (25.4%)
Serious TEAE	29 (14.3%)	21 (10.4%)
Any treatment-related TEAE (TRAE)	18 (8.9%)	19 (9.5%)
Most common (≥2%) TRAE Constipation	10 (4.9%)	11 (5.5%)
Serious TRAE	0	0
Any TRAE leading to discontinuation	1 (0.5%)	0
Any TRAE resulting in death	0	0

Conclusions: Intravenous NEPA was shown to be safe and well-tolerated with a similar safety profile to oral NEPA in patients with various solid tumors receiving HEC.

Clinical trial identification: NCT02517021

Legal entity responsible for the study: Helsinn Healthcare, SA

Funding: Helsinn Healthcare SA

Disclosure: L. Schwartzberg: Served as a consultant for Helsinn, Tesaro, Eisai, and Merck and have received research funding from Helsinn and Tesaro. D. Voisin, G. Rizzi: Employee of Helsinn Healthcare. M. Karthaus: Served as and received honoraria for being a consultant for Helsinn and Riemser. All other authors have declared no conflicts of interest.

1548PD Quality of life (QOL) evaluation of patients in a phase 3 study comparing NEPA with an aprepitant regimen for prevention of chemotherapy-induced nausea and vomiting (CINV)

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Background: Suboptimal CINV prevention can negatively impact patients' (pts) QOL by interfering with daily functioning. Antiemetic guidelines recommend co-administration of a NK_1 receptor antagonist (RA)/5-HT_3RA/corticosteroid to optimize CINV control in pts at high risk for CINV. NEPA, a fixed combination of the NK_1RA netupitant and 5-HT_3RA palonosetron (PALO) has shown superior CINV prevention and improvement in QOL over PALO. A single dose of NEPA recently showed non-inferiority to a 3-day aprepitant/granisetron (APR/GRAN) regimen in preventing CINV in the first head-to-head comparison of NK_1RA-containing regimens. The impact of CINV on pts' QOL in this study was explored.

Methods: This randomized, double-blind, Phase 3 study in chemotherapy-naïve pts receiving cisplatin-based chemotherapy (CT) assessed the non-inferiority of NEPA versus APR/GRAN for complete response (CR: no emesis/no rescue medication [RM])

Table: 1548PD

% Patients	NEPA (N = 412)	APR/GRAN (N = 416)	Risk Difference (95% CI)
NIDL (overall domain) Acute (0-24h) Delayed (25-120 h)	86.2% 76.0%	83.2% 70.7%	3.3 (-1.6%, 8.1%) 5.8% (-0.1%, 11.8%)
NIDL (nausea domain) Acute Delayed	81.8% 71.1%	80.0% 65.1%	2.0% (-3.3%, 7.3%) 6.5% (0.2%, 12.8%)*
NIDL (vomiting domain) Acute Delayed	87.9% 81.3%	86.8% 77.4%	1.4% (-3.1%, 5.9%) 4.5% (-1.0%, 9.9%)
No Emesis Acute Delayed	85.2% 79.4%	87.5% 76.2%	−2.2% (-6.9%, 2.4%) 3.3% (-2.4%, 8.9%)
NSN Acute Delayed	89.8% 78.2%	87.3% 72.8%	2.6% (-1.7%, 6.9%) 5.4% (-0.4%, 11.2%)
No RM Acute Delayed	98.8% 97.6%	98.3% 94.7%	0.5% (-1.2%, 2.1%) 2.9% (0.2%, 5.5%)*

*statistically significant difference NEPA: fixed combination netupitant/palonosetron, APR: aprepitant, GRAN: granisetron, NIDL: no impact on daily life, NSN: no significant nausea, RM: rescue medication

rates during the overall (0-120 h) phase post-CT. All pts received dexamethasone on days 1-4. Secondary endpoints included proportion of pts with no emesis, no significant nausea (NSN: <25mm on 100mm VAS), no RM use, and no impact on daily life (NIDL) as assessed by the Functional Living Index—Emesis (FLIE), comprised of vomiting- and nausea-specific questions/domains. The Cochran-Mantel-Haenszel test was used for between group comparisons; non-inferiority testing was not done for secondary endpoints.

Results: Treatment groups were similar for the 828 pts analyzed: male (71%); mean age 55 years; lung cancer (58%). NIDL rates were higher for NEPA, particularly during the delayed phase; similar results were seen for no emesis, NSN, and no RM.

Conclusions: In this first study comparing NK_1RA regimens, NEPA administered only on day 1 was numerically similar to a 3-day oral APR/GRAN regimen in maintaining functional status in patients receiving highly emetogenic CT.

Legal entity responsible for the study: Helsinn Healthcare, SA

Funding: Helsinn Healthcare

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1549PD Multicenter randomized controlled trial to evaluate the efficacy of frozen gloves for the prevention of chemotherapy-induced peripheral neuropathy

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Background: Chemotherapy-induced peripheral neuropathy (CIPN) is a common side effect of oxaliplatin and taxanes with a negative impact on quality of life (QOL). This study investigates the efficacy of wearing frozen gloves (FGs) during chemotherapy for the prevention of CIPN due to oxaliplatin or taxanes and the influence on patients' QOL.

Methods: Patients with newly diagnosed cancer starting treatment with oxaliplatin, docetaxel or paclitaxel were eligible for this multicenter randomized controlled trial. Patients were randomized between wearing FGs on both hands during treatment or not wearing FGs. Self-reported CIPN and QOL were measured with the validated EORTC-QLQ CIPN20 and EORCT-QLQ C30 at four time points; baseline (T0), after three cycles (T1), end of chemotherapy (T2) and after 6 months (T3). Subscales were analyzed with analysis of covariance and neuropathy symptoms with logistic regression analysis.

Results: Between February 2013 and May 2016, 180 patients were included, 90 patients in both arms. Thirty-one patients (34%) discontinued the FGs before end of chemotherapy mainly due to discomfort. Intention to treat analyses showed that patients in the FG-group experienced less tingling in fingers/hands at T1 (11% vs. 24%; p=.009) and T2 (28% vs. 43%, $p = 0.038$) compared to controls. At T3 these differences disappeared (28% vs 24%, p=.0884). FG patients also experienced a trend towards less interference in handling small objects (2% vs 10%, $p = 0.06$) and opening a bottle (9% vs. 6%, $p = 0.06$) at T1. FG patients also reported significantly lower motoric problems (mean 8.3 (SD 9.7) vs. 12.8 (SD 13.6), $p = 0.013$) compared to controls at T1. At T1, those treated with FGs reported statistically significant better QOL on EORTC QLQ-C30 subscales physical (mean 82 vs.74), role (mean 66 vs. 51), cognitive (mean 85 vs. 78), and social functioning (mean 79 vs. 67), and symptom scales fatigue (mean 40 vs. 49) and appetite loss (mean 21 vs. 34), all $p < 0.05$.

Conclusions: No long-term differences in neuropathy were found, but FGs reduced neuropathy symptoms with better QOL during chemotherapy. Future studies should focus on the biological process of cooling to prevent CIPN.

Clinical trial identification: NL39650.015.12

Legal entity responsible for the study: G. Vreugdenhil

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1550P Primary prevention of nausea and vomiting induced by moderately emetogenic chemotherapies: findings from the French CONVINCE-ME survey

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Background: Despite the considerable progress achieved in the last 30 years vomiting and especially nausea continue to be two of the most distressing side-effects of cancer chemotherapy. The objective of this survey was to assess the compliance of anti-emesis prescriptions with the ESMO 2016 and French AFSOS 2013 guidelines (French speaking association for supportive care in cancer), in primary prophylaxis of moderately emetogenic chemotherapies (MEC) as defined by ESMO guidelines.

Methods: Between February and November 2016, 35 pharmacists and 41 nurses from 35 French centers specialized in cancer treatment completed a 13-item questionnaire drawn up by a scientific committee about their anti-emesis practices. Concurrently, the nurses at each center recorded prospectively treatments prescribed to 10 to 20 patients starting the first cycle of MEC.

Results: Data were gathered on 448 patients with gastrointestinal cancers and 166 with lung cancers; 29% and 47% of all patients were treated with carboplatin or oxaliplatin respectively. The most frequent CINV preventive treatments for the acute phase were the combination of 5HT3 antagonist + corticoid (52% of patients) and the combination of 5HT3 antagonist + corticoid + anti-NK1 (33%). For the delayed phase, 5HT3 antagonist only (23%), anti-NK1 only (17%) and the combination of 5HT3 antagonist + anti-NK1 (17%) were the most prescribed treatment. Overall, 49% and 33% of patients in the acute phase and 10% and 17% in the delayed phase were treated in compliance the ESMO and AFSOS guidelines respectively.

Conclusions: The CONVINCE-ME survey shows inadequate use of existing recommendations at specialized centers and highlights the need for improved understanding and guideline application.

Legal entity responsible for the study: Florian Scotté

Funding: MSD

Disclosure: F. Scotté: Roche, Vifor, MSD, Teva, Norgine, Prostrakan, Leo pharma, Janssen, Hospira, Boehringer, Sanofi, Amgen, Pierre Fabre Oncologie, Tesaro. H. Bertucat: MSD. All other authors have declared no conflicts of interest.

1551P Risk factors of chemotherapy-induced nausea and vomiting during cisplatin regimen in antiemetic triplet regimen including palonosetron or granisetron: TRIPLE study (phase III)

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Background: Current antiemetic guidelines recommend antiemetic triplet regimen for cisplatin-based chemotherapy. Although several prior studies have identified risk factors for chemotherapy-induced nausea and vomiting (CINV), only a few have evaluated antiemetic triplet regimen, particularly with palonosetron. Therefore, the purpose of the present study was to confirm and compare the risk factors for CINV when using palonosetron or granisetron.

Methods: A total of 825 patients in the phase III clinical trial on cisplatin regimen were evaluated. The primary endpoint was complete response (CR) rate in the overall period (0–120 h). All patients were evaluated for CINV risk factors. Using a post-hoc analysis, the impact of antiemetic treatment on CR was assessed, and odds ratio (OR) with 95% confidence intervals (CIs) for antiemetic treatment failure were evaluated by using multivariate logistic regression models. CINV risk factors were also evaluated separately in each treatment group.

Results: The multivariate analysis revealed that female (OR: 2.572; 95% CI: 1.855–3.566), less than 60 years old (OR: 1.717; 95% CI: 1.252–2.355), the cisplatin dosage (OR: 1.017; 95% CI: 1.001–1.033), and granisetron use (OR: 1.357; 95% CI: 1.013–1.817) were all significantly associated with antiemetic treatment failure in the entire

study group. Similarly, female and age were also identified as the risk factors associated with treatment failure in both groups ($P < 0.0001$). Kaplan–Meier plots of time to event classified each treatment group and revealed no significant difference between the groups for patients with zero risk factors ($P = 0.353$). For patients with one or more risk factors, those treated with palonosetron experienced significantly higher CR rates than those treated with granisetron ($P = 0.049$).

Conclusions: This analysis revealed risk factors of CINV when using triplet antiemetic regimen Including palonosetron or granisetron for cisplatin. Palonosetron might be preferred for patients with one or more risk factors.

Clinical trial identification: Clinical trial information: UMIN 000004863 *UMIN: University Medical Information Network

Legal entity responsible for the study: Pharma Valley Center, Shizuoka Organization for Creation of Industries

Funding: Pharma Valley Center, Shizuoka Organization for Creation of Industries

Disclosure: T. Yamanaka: Reserch Funding: Taiho. K. Goto: Taiho, Chugai, Ono. N. Yamamoto: Consulting or Advisory Role: Chugai Pharmaceutical Co, Ltd, Ono Pharmaceutical Co. Ltd, Research Funding: Ono Pharmaceutical Co., Ltd, Taiho Pharmaceutical Co., Ltd. All other authors have declared no conflicts of interest.

1552P Evaluation of Antiemetic Practices for Prevention of Chemotherapy-induced Nausea and Vomiting (CINV): Results of a European Oncology Nurse Survey

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Background: Preventing CINV in most patients is possible when guideline-recommended prophylactic antiemetics are utilized. Because oncology nurses play a critical role in risk assessment and management of CINV, a survey of European nurses was conducted to evaluate antiemetic practices, determine awareness of and adherence to current guideline recommendations, and explore barriers to adherence.

Methods: Between March 2016 and March 2017, 212 oncology nurses in 16 European countries completed a 20-question online survey.

Results: Respondents had 15 years (median) experience as an oncology nurse and most were able to suggest or prescribe antiemetics. Most (n = 169, 80%) worked in the public not-for-profit hospital setting, seeing both in- and outpatients (n = 107, 50%). While nurses were most familiar with ASCO (n = 97, 46%) and MASCC/ESMO (n = 84, 40%) guidelines, individual institution guidelines were used most (n = 99, 47%). Key discrepancies between antiemetic use and guideline recommendations were: i) under-utilization of NK_1RAs, 5-HT_3RAs and a steroid on Day 1 in the HEC setting and ii) high use of 5-HT_3RAs during days 2-5 when guidelines recommend a steroid (Table 1). Metoclopramide use (not guideline recommended) was also high, with ~30% and ~50% of nurses reporting usage for acute and delayed phases, respectively, for both HEC and MEC settings. The most common barrier to the use of guideline-recommended agents was reported as physician preference (n = 84, 40%). Product cost and formulary inclusion also played a role. The 2 most common challenges in managing CINV were "controlling nausea and vomiting in the delayed phase" (n = 135, 64%) and "reducing the impact of CINV on patients' quality-of-life" (n = 130, 61%).

Conclusions: This survey highlights many opportunities to improve utilization of guideline-recommended antiemetics, thereby optimizing prevention of CINV and quality-of-life for patients receiving emetogenic chemotherapy.

Legal entity responsible for the study: Helsinn Healthcare SA

Funding: Helsinn Healthcare, SA

Disclosure: P. Dielenseger: Member of advisory boards of Helsinn, Bayer Healthcare, Pfizer, Shire, Tesaro, Janssen, and BMS A. Young: Received honorarium from MSD (advisory board and presentations given), Helsinn (advisory boards) and Chugai (presentation given). P. Jahn: Support includes travel support: Helsinn (2014); Current consulting or advisory role: Bristol-Myers Squibb, Chugai, Norgine, and Clinigen; Clinical Research Fund by Chugai. All other authors have declared no conflicts of interest.

1553P A pooled analysis evaluating the combination antiemetic therapy on chemotherapy-induced nausea and vomiting in patients with colorectal cancer receiving oxaliplatin-based chemotherapy of moderate emetic risk

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Background: The incidence and risk factor of delayed chemotherapy-induced nausea and vomiting (CINV) for colorectal cancer (CRC) patients receiving oxaliplatin-based chemotherapy has not been clearly controlled. To evaluate the efficacy and risk factor of combination antiemetic treatment for delayed CINV in CRC patients receiving oxaliplatin-based chemotherapy.

Methods: Aggregated data were pooled from the two prospective observational studies and one clinical trial; A nationwide survey of CINV study group, the other prospective observational study in Japan and SENRI Trial in Japan. We assessed whether delayed CINV were controlled with 3 antiemetic treatment. We also evaluated risk factors by logistic regression analysis.

Results: A total of 661 patients were evaluable in this study. The median age was 64 (range:19-85) with 391males and 270 females. Three antiemetics were used in 220 (33.3%) patients. Delayed CINV were experienced more commonly in women than in men. Delayed nausea was well controlled with 3 antiemetics than with 2 antiemetics for women (38.3% vs. 52.8%; P=0.0295). Delayed vomiting was well controlled with 3 antiemetics than with 2 antiemetics for overall (4.1% vs. 15.9%; P<0.0001) and for women (5.3% vs. 24.4%; P<0.0001). We identified several risk factors; women (odds ratio [OR], 1.853; 95% confidence interval [CI], 1.326 to 2.591; P=0.0003), motion sickness (OR, 1.947; 95%CI, 1.230 to 3.082; P=0.0044) and age (OR, 0.976; 95%CI, 0.961 to 0.991; P=0.0020) for delayed nausea, and women (OR, 2.447; 95%CI, 1.475 to 4.059; P=0.0005), motion sickness (OR, 1.892; 95%CI, 1.024 to 3.494; P=0.0417), 2 antiemetics (OR, 4.890; 95%CI, 2.362 to 10.122; P<0.0001) and FOLFOX regimen (OR, 1.680; 95%CI, 1.028 to 2.747; P=0.0384) for delayed vomiting.

Conclusions: Three antiemetics combination are encouraged for CRC female patients treated with oxaliplatin-based chemotherapy to alleviate delayed CINV. Identification of individual risk factors will assist in the development of personalized treatments for delayed CINV.

Legal entity responsible for the study: N/A

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Disclosure: All authors have declared no conflicts of interest.

Table: 1552P Antiemetic Utilization - European Nurse Survey

Setting	Antiemetic Class	Antiemetics Utilized n (% respondents)	
		Acute Phase (0-24 h)	Delayed Phase (25-120 h)
HEC	5-HT_3 RA NK_1 RA NEPA Steroid (eg, DEX)	171 (81%) 130 (61%) 48 (23%)	105 (50%) 92 (43%) 23 (11%) 133 (63%)
	Phenothiazine Benzodiazepine	173 (82%) 1 (0%) 35 (17%)	12 (6%) 25 (12%) 19 (9%) 103 (49%)
	Antipsychotic Metoclopramide	10 (5%) 63 (30%)	
MEC	5-HT_3 RA NK_1 RA NEPA Steroid (eg, DEX)	183 (86%) 44 (21%) 17 (8%)	100 (47%) 38 (18%) 19 (9%) 122 (58%)
	Phenothiazine Benzodiazepine	164 (77%) 3 (1%) 14 (7%) 5	10 (5%) 15 (7%) 13 (6%) 108 (51%)
	Antipsychotic Metoclopramide	(2%) 67 (32%)	

HEC: highly emetogenic, MEC: moderately emetogenic, DEX: dexamethasone, NEPA: fixed combination of netupitant/palonosetron

1554P Efficacy of neurokinin-1 receptor antagonists in the prevention of Chemotherapy-Induced Nausea and Vomiting in patients receiving carboplatin-based chemotherapy: a systematic review and meta-analysis

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Background: According to current ESMO – MASCC guidelines, a combination of a neurokinin-1 receptor antagonist (NK1RA), dexamethasone and a 5-HT3 receptor antagonist (5-HT3RA) is recommended to prevent carboplatin-induced emesis, with moderate level of confidence and not unanimous consensus. Our aim was to perform a meta-analysis of all randomized trials (RCTs) evaluating the role of a NK1RA in the prevention of emesis for patients receiving carboplatin.

Methods: A systematic review was performed in January 2017, including RCTs comparing NK1RA + dexamethasone + 5-HT3RA vs. dexamethasone + 5-HT3RA in patients receiving first cycle of carboplatin-based chemotherapy. Primary outcome was complete response (CR), defined as no emesis and no use of rescue medication. CR was measured in day 1 (acute phase), days 2-5 (delayed phase) and days 1-5 (overall period). A random effects model was applied.

Results: 9 trials were potentially eligible (7 aprepitant, 1 fosaprepitant, 1 rolapitant): 6 were RCTs including only patients receiving carboplatin, and 3 were subgroup analyses of patients receiving carboplatin within RCTs including various moderately emetogenic regimens. Data of CR were available in 8 trials (1598 patients). Addition of NK1RA improves CR in all phases: acute phase, 94.5% vs. 90.1% (Odds Ratio 1.75, 95%CI 1.19-2.59, $p = 0.005$); delayed phase, 76.4% vs. 61.7% (Odds Ratio 2.04, 95%CI 1.64-2.55, $p < 0.0001$); overall period, 75.3% vs. 60.4% (Odds Ratio 2.04, 95%CI 1.64-2.54, $p < 0.0001$). There was no significant heterogeneity among trials. Sensitivity analyses, performed excluding subgroup analyses and excluding open-label trials, produced similar results.

Conclusions: In patients receiving carboplatin-based chemotherapy, triple antiemetic therapy with NK1RA, dexamethasone and 5-HT3RA is associated with a statistically significant and clinically relevant improvement in CR, compared to 5-HT3RA plus dexamethasone. Individual patient data meta-analysis could help to identify patients who are likely to obtain the highest improvement from the addition of NK1RA.

Legal entity responsible for the study: Massimo Di Maio

Funding: None

Disclosure: M. Di Maio: Roles as advisor, and speaker's fee for Merck Sharp & Dohme, AstraZeneca, Bayer, Janssen, Bristol Myers Squibb, and Eli Lilly. E. Bria: Roles as advisor, and speakers' fee for Merck Sharp & Dohme, AstraZeneca, Celgene, Pfizer, Eli-Lilly, Bristol Myers Squibb, and Novartis. All other authors have declared no conflicts of interest.

1555P Pharmacokinetic (PK) study of a single oral dose of NEPA in Chinese healthy volunteers (HVs)

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Background: NEPA, a combined neurokinin-1 receptor antagonist (RA) netupitant (NETU; 300 mg) and 5-HT_3–RA palonosetron (PALO; 0.50 mg), is the first approved oral combination antiemetic. NEPA has shown superior efficacy over PALO in preventing chemotherapy-induced nausea and vomiting (CINV), in cisplatin and AC-chemotherapy settings, leading to its approval in the US and Europe (with 85% of patients Caucasian in the clinical trials). A recent phase 3 registration trial in Asian patients demonstrated non-inferiority of a single oral dose of NEPA in preventing CINV compared with a 3-day oral aprepitant/granisetron regimen. The present study was undertaken to assess the PK profile of NETU and PALO in Chinese HVs.

Methods: Eligible HVs received a single oral dose of NEPA administered as a hard gelatin capsule on day 1, after 10-h fasting. Blood samples for PK analysis were collected pre-dose and at 1, 2, 3, 4, 4.5, 5, 5.5, 6, 8, 12, 24, 48, 72, 96, 120, 144, 168, 192, and 240 h post-dose. The plasma concentration of NETU and PALO was determined by liquid chromatography-tandem mass spectrometry (LC-MS/MS). PK parameters were estimated via non-compartmental analysis using the WinNonlin 6.3 software (Certara Inc., Princeton, NJ, USA).

Results: A total of 18 subjects were enrolled (16 male; median body weight 62.7 kg [52.6–75.2 kg]; median age 27 y [21–37 y]). After a single oral dose of NEPA, mean (±SD) values of peak plasma concentration (C_{max}) for NETU were 698±217 ng/mL at a median of 4.5 h (T_{max}; 3–6 h), with mean (±SD) overall exposure up to the last measurable concentration (AUC_{0-t}) of 20.2±3.93 h*mg/L. PALO plasma concentrations reached mean (±SD) C_{max} of 1800±252 ng/mL at 3 h (2–6 h) with mean (±SD) AUC_{0-t} of 77.6±13.3 h*µg/L. NEPA was well tolerated in all HVs.

Conclusions: In Chinese HVs the PK profile of NETU was comparable to that previously observed in Caucasians. For PALO, C_{max} and AUC_{0-t} were higher in these Chinese HVs compared to Caucasians, which may be explained by CYP2D6 (involved in the metabolism of PALO) polymorphism. However, the similar efficacy and safety for PALO and NEPA in pivotal studies in both populations suggests that the higher exposure to PALO in Chinese HVs is unlikely to be clinically relevant.

Legal entity responsible for the study: Helsinn Healthcare SA

Funding: Helsinn Healthcare SA

Disclosure: S. Chessari, C. Lanzarotti, A. Bernareggi: Helsinn Healthcare SA employee

All other authors have declared no conflicts of interest.

1556P Iron deficiency anaemia in oncology: an epidemiological prospective study

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Background: Anaemia in oncology is frequent, decreasing quality of life and prognosis. Its causes are multiples and still largely unknown, among them, iron deficiency (ID) is seldom studied. Associated with inflammatory syndrome, ID leads to the sequestration of iron in macrophage, making it unavailable for erythropoiesis. Prevalence of ID needs to be specified in oncology as it could be easily corrected by intravenous iron, avoiding use of EPO or blood transfusion and their side effects.

Methods: In this prospective, multicentre cohort study (NCT01968304), anaemia and ID were evaluated in patients with locally advanced or metastatic solid tumour and lymphoma newly diagnosed before starting a chemotherapy regimen. Blood samples were collected at the inclusion (week 0 - W0), 6 weeks (W6) and 12 weeks (W12) after. Prevalence was evaluated for both functional ID (FID) and absolute ID (AID) in the general population and according to the tumours location. ID was correlated with tumour response (RECIST criteria).

Results: 129 patients were enrolled between 2013 and 2015. 119 had solid tumours (breast 36, colorectal 27, lung 28, prostate 12, others 16) and 10 had lymphomas (not shown).

Table: 1556P

Location N (%)	Anaemia N (%)			Functional iron deficiency N (%)			Absolute iron deficiency N (%)			Functional ID associated with Anaemia N (%)		
	W0	W6	W12	W0	W6	W12	W0	W6	W12	W0	W6	W12
Breast 36 (30)	13 (36.1)	20 (64.5)	17 (63.0)	15 (41.7)	20 (64.5)	2 (5.6)	1 (3.2)	2 (7.4)	6 (16.7)	11 (35.5)	11 (35.5)	9 (33.3)
Colorectal 27 (23)	20 (74.1)	16 (72.7)	11 (68.8)	14 (51.9)	8 (36.4)	5 (18.5)	3 (13.6)	2 (12.5)	10 (37.0)	10 (37.0)	6 (27.3)	5 (31.2)
Lung 28 (24)	16 (57.1)	22 (88.0)	14 (93.3)	13 (48.1)	8 (32.0)	1 (3.7)	0 (0.0)	0 (0.0)	8 (29.6)	8 (29.6)	8 (32.0)	4 (26.7)
Prostate 12 (10)	9 (75.0)	11 (91.7)	9 (81.8)	6 (50.0)	3 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (33.3)	4 (33.3)	2 (16.7)	2 (18.2)
All solid tumours 119 (100)	63 (52.9)	75 (72.8)	56 (71.8)	62 (48.0)	49 (43.0)	9 (7.0)	5 (4.0)	4 (5.0)	32 (26.9)	32 (26.9)	32 (31.1)	23 (29.5)

At W0, 62 patients (48%) had FID, 32 (26.9%) had FID associated with anaemia and 9 (7%) had AID. FID prevalence remains constant from W0 to W12, so as FID anaemia and AID. Also, ID incidence remains constant between W6, 17 (15.2%) and W12 10 (11.6%). Localization was not correlated with FID or FID anaemia but prevalence of AID is higher for colorectal tumours. ID (evaluated at W12) was significantly correlated ($p = 0.04$) with tumour response at W12, 51.2% of responders among patients with no ID versus only 33.3% among patients with ID.

Conclusions: Our data confirm the high prevalence of ID in cancer patients. Localization is not correlated with the prevalence of ID whereas absolute ID is of higher rate in colorectal cancer. Also, ID at W12 without supplementation seems to be predictive of chemotherapy response.

Clinical trial identification: NCT01968304. Release date: October 1, 2013

Legal entity responsible for the study: Centre Antoine Lacassagne

Funding: Vifor Pharma France

Disclosure: All authors have declared no conflicts of interest.

1557P Nutritional risk as a predictor of short-term outcomes in a prospective cohort of elderly patients with cancer

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Background: To determine if the nutritional risk identified by the Mini NutritionalAssessment Short-Form (MNA®-SF) is an independent predictor of short-term outcomes (infection, hospitalization and premature death).

Methods: prospective cohort study of elderly patients (≥60 years) with a recent diagnosis of cancer admitted to an outpatient oncology unit was performed. Sociodemographic and clinical variables and MNA®-SFwere collected at baseline. The outcomes were healthcare-associated infection, hospitalization and death. Data were analysed using the multivariateCoxproportional hazards models. Overall survival was estimated using the Kaplan–Meier method and survival curves were compared using theLog rank test.

Results: he cohort consisted of 608 elderly patients followed for 180 days. The mean age was 71.9 years (range: 60–96) and 50.2% participants were at risk of malnutrition as measured by the MNA®-SF. During follow-up, 35.5% of participants were hospitalized, 29.4% had healthcare-associated infections and 16.4% died. After adjustment for age, site and stage of cancer, the multivariate regression Cox model showed that being undernourished was an independentpredictor of infection (adjusted Hazard Ratio [aHR]=1.88, 95%CI 1.32–2.67, $p < 0.001$) hospitalization (HR = 1.5, 95% CI:1.10–2.06, $p = 0.012$) and death (HR = 3.12, 95% CI: 1.74–5.78, $p < 0.001$).

Conclusions: Nutritional risk at admission was identified as a significant predictor of risk forpremature death, infection, and need for hospitalization in elderly cancer patients. The use of MNA®-SF should be incorporated into regular geriatric assessment of olderpatients with cancer.

Legal entity responsible for the study: Jurema Telles De Oliveira Lima

Funding: FACEPE CNPQ

Disclosure: All authors have declared no conflicts of interest.

1558P A patient-centered approach to the re-development of supportive care services for oncology adolescent and young adult (AYA) patients (pt(s)) across McGill University hospitals (Rossy Cancer Network-RCN)

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Background: Most AYA pts (age 18-44) across the RCN are seen in adult oncology settings tailored to the medical and supportive care needs of the general cancer population. The purpose of this study is to conceptually re-develop the delivery of supportive care services to this pt population and create a care model that could be used as a framework for AYA clinics in Canada and abroad.

Methods: An analysis of the Ambulatory Oncology Patient Satisfaction Survey (AOPSS) 2012-2015 was conducted to better understand AYAs' satisfaction with the current level of care in RCN. A Chi-square test was employed to investigate differences between AYAs (ages 18-34 vs 35-44) and pts age 45 and over (n = 2,438).

A Delphi study, composed of two panels (pts vs. health care professionals), was conducted. Panelists were asked to select a set of strategies proposed by Zebrack et al. (2010) to address the service gaps identified through AOPSS. Selection was made by rank ordering strategies based on scores of importance (7 point Likert scale). Analysis of variance (ANOVA) was used to examine study results.

Results: The analysis of the AOPSS results revealed important differences related to i) the overall satisfaction and perception of quality of care; ii) access to services and iii) satisfaction with specific aspects of care such as emotional support, communication, access to information and physical comfort.

Both Delphi panels have identified access to 1) age-appropriate education programs; 2) standardized symptom management, pain control, palliative care; and 3) fertility preservation as important strategies to enhance delivery of supportive care services to AYAs (Table).

Conclusions: Evidence gathered through the AOPSS and Delphi studies will be used to inform health administrators of strategies needed to better respond to the unique supportive care needs of oncology AYAs.

Legal entity responsible for the study: Petr Kavan

Funding: Rossy Cancer Network

Disclosure: All authors have declared no conflicts of interest.

1559P Multidimensional telemonitoring of cancer patients (pts) receiving chronomodulated (chrono) Irinotecan (I), 5-fluorouracil (F), leucovorin (L) and oxaliplatin (O; chronoIFLO4) combination at home

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Background: FOLFIRINOX is an active yet toxic regimen against intestinal cancers. Improving its tolerability could widen its use in routine clinical practice. Circadian-based chrono administration of this triplet can be performed using a multichannel programmable-in-time pump. Here, we show the safety of chronoIFLO4 at home, through real-time multidimensional telemonitoring of circadian rest-activity rhythm (CircAct), sleep, patient-reported outcome measures (PROM) and body weight changes (BWC) using 1st generation e-Health platform inCASA.

Methods: Pts received Day (D)1 chrono I (180 mg/m2, over 6-h; peak rate at 5:00), and D 2-4 chrono O (25 mg/m2/d, over 11.5-h; peak rate at 16:00) and F-L (800 mg/m2/d and 400 mg/m2/d, respectively, over 11.5-h; peak rate at 04:00), q2 weeks at home. Pts completed the 19-item MD Anderson Symptom Inventory (MDASI) on an interactive electronic screen, weighed themselves on a dedicated scale, and continuously wore a watch-sized wrist-accelerometer for CircAct and sleep monitoring. Daily data were securely teletransmitted via Internet to a specific server accessible by the hospital team. The validated and clinically-relevant CircAct parameter I<O and sleep efficiency (SE) were calculated. The dynamic patterns over time of PROMs, BWC, I<O and SE inform the oncology team on tolerance in real time.

Table: 1558P Sample Strategies for Improving Patient Quality of Life and Quality of Care Throughout the Cancer Care Continuum (Zebrack et al, 2010)

	Patient Panel (n = 31)		Health Care Professionals Panel (n = 31)	
	Rank Order (round 1)	Importance Score (0-7 Likert scale)	Rank Order (round 1)	Importance Score (0-7 Likert scale)
Patient education programs that provide AYAs with knowledge regarding treatment options and the potential physical and QOL implications of cancer therapy	1	6.55	4	6.45
Inform reproductive-age patients of cancer- related fertility risks as early in the treatment planning as possible (as per ASCO guideline) and refer as needed to an appropriate fertility preservation specialist	2	6.42	2	6.58
Provide access to a systematic and standardized symptom management, pain control, and palliative care program	3	6.35	1	6.65

Results: Eleven patients (48-72 years; 45% males; 27% PS = 0) received 26 cycles (cy) of chronoIFLO4, and provided 5,891 data points/8,736 expected (67.4%). No grade 3-4 clinical toxicity occurred. The most severe MDASI scores remained low: interference with work (mean: 5.1/10) or general activity (4.9); fatigue (4.9); distress (4.2) and appetite loss (3.6). Mean BWC was -0.9% and mean SE remained above 82%. CircAct disruption (I<O $\leq$97.5%) was observed in 4 (15%) cys before chronoIFLO4 start and in 5 (19%) cys at D14.

Conclusions: ChronoIFLO4 represents a safe therapeutic option at home, and the pt-centered multidimentional telemonitoring solution allows the design of innovative management approaches, ultimately improving pt experience with chemotherapy, safety and outcomes.

Legal entity responsible for the study: INSERM and European Commission

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1560P A pilot study to evaluate the feasibility, usability, and perceived satisfaction with eCO (eCediranib-Olaparib), a mobile application for side effect monitoring and reporting, in women with recurrent ovarian cancer

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Background: Cediranib inhibits VEGFR1-3 with significant but treatable side effects of hypertension and diarrhea. High frequency of these events occurred in a trial of cediranib with olaparib (C+O). Effective control of these side effects is therefore important for C+O therapy. eCO, a cloud-based mobile medical device, was developed to provide secure capture, storage, and transmission of accurate BP and diarrhea data to aid in remote monitoring. Pts receive automated reminders and instructions for self-management based on severity. HCPs monitor pt status via a secure web portal and email alerts.

Methods: Pts enrolled in a Ph 2 study of C+O (NCT02345265) could opt to participate in this pilot study. Pts received eCO-based prompts, used eCO to record BP via a Bluetooth-linked BP cuff and to enter diarrheal events, and received eCO-based reminders and recommendations. Pts completed a 17-item usability and satisfaction questionnaire after 4 weeks of eCO use. The primary objective was to evaluate the feasibility, usability, and satisfaction of eCO use. Data were analyzed by Wilcoxon Rank Sum Analysis.

Results: 15 pts completed the pilot study. Pts indicated they felt closely monitored, connected with the healthcare team, involved in their own care, and satisfied with ease of learning and use of many eCO functions (alpha < .01). Pts were satisfied with diarrhea entry and finding past recommendations (alpha < .05) and were not satisfied with reporting diarrhea side effects. eCO captured 98.1% of expected BP values (94.2% direct upload; 5.8% manual entry). BP events ($\geq$2 consecutive BP > 140/90 mmHg) occurred in 11 pts (6 with 1 event, 2 with 2 events, 3 with 3 events) with median duration 5 days (range 3-28 days). 12 pts reported 20 diarrhea events (range 1-4 events); median duration was 1.4 days (range 1.0-2.7 days); 31 entries were made (28 Gr 1, 3 Gr 2).

Conclusions: In this initial pilot, eCO captured accurate BP and diarrhea events from pts for remote monitoring. Pts reported overall usability and satisfaction with eCO, especially feeling closely monitored, more connected, involved in self-care and ease-of-use. Use of eCO in other studies is planned.

Clinical trial identification: NCT02345265

Legal entity responsible for the study: National Cancer Institute

Funding: National Cancer Institute

Disclosure: J. Liu: Served on a Scientific Advisory Board and Consultant for AstraZeneca. D.M. O'Malley: Scientific Advisory Board for AstraZeneca E. Strock, R. Phillips: Employee of Voluntis, Inc. K. Mari: Consultant/advisory role to Voluntis, Inc. B. Killam: Consulting/advisory role to AstraZeneca All other authors have declared no conflicts of interest.

1561P Study of the satisfaction level of an education program for cancer patients

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Background: As the demand for cancer patient education has increased lately, the administrative body of the universal health insurance in South Korea has decided to include the cost for cancer patient education to its insurance coverage. Dongnam Institute of Radiological Medical Sciences (DIRAMS) in Busan, South Korea, created its cancer patient education program in 2016 and has educated cancer patients about their treatments according to the program since then. This paper will discuss the study conducted at the hospital in order to estimate the level of satisfaction among the patients who participated in the education program.

Methods: The program consists of an 80-minute long education session led by a doctor, a nurse, and a clinical dietitian before each cancer patient receives his or her chemotherapy, radiation therapy, or a surgery. questionnaire survey was conducted on patients who participated in the education program from July 2016 to March 2017.

Results: Among the patients who participated in the survey, the number of patients who had chemotherapy education is 663. Stomach cancer was the most prevalent cancer type in this group, followed by cholangiocarcinoma. 75.3% of the patients in this group received palliative chemotherapy, and the rest received adjuvant chemotherapy. The satisfaction level of the chemotherapy education was 4.98 on a five-point Likert scale. The number of patients who had the radiotherapy education was 195. Breast cancer represents the largest portion in this group. The satisfaction level of the radiotherapy education was 4.3. The number of patients who received the surgery education was 70. The satisfaction level of the surgery education was 4.6.

Conclusions: The total 928 patients who participated in the education program rate their level of satisfaction as 4.8 in average on a scale of 1 to 5. This high rating can be seen as an indication of high satisfaction in the quality of the education about their treatments. To enhance the education program further, it will be worthwhile to investigate improvements in each part of the program and in the perspective of patients. Subsequently, it is also worthwhile to investigate how the education program affects cancer patients.

Legal entity responsible for the study: Ha Young Lee

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1562P Factors influencing the use of thromboprophylaxis in cancer outpatients: CAT AXIS, a case-vignette study on clinical practice

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Background: Data on long-term venous thromboembolism (VTE) prophylaxis in cancer outpatients remain scarce. In the absence of consistent treatment guidelines, our objective was to describe clinical practice and to identify factors influencing the use of thromboprophylaxis.

Methods: CAT AXIS was a multicenter cross-sectional study based on the completion of physician-profile questionnaires and the assessment of 10 e-mailed credible clinical scenarios of lung, colon and breast cancer by each of participants using the case-vignettes validated method.

Results: A total of 224 physicians participated allowing the completion and the analysis of 2,085 case vignettes corresponding to 765, 703 and 617 fictive clinical scenarios on lung, colon and breast cancers, respectively. The overall rate of thromboprophylaxis was 680/2085 (32.6%) among participants with a comparable proportion for the three types of cancer. Low-molecular-weight heparin (LMWH) was the most frequently used, by 92.7%, 93.8% and 83.9% of participants for lung, colon and breast cancer, respectively; treatment duration of $\geq$ 3 months was prescribed by 74.4% of participants. Multivariate analysis of factors influencing thromboprophylaxis based on patient's characteristics is summarized in Table.

Table: 1562P Factors influencing the prescription of thromboprophylaxis

	Lung cancer		Colon cancer		Breast cancer	
	OR [95% CI]	p	OR [95% CI]	p	OR [95% CI]	p
ECOG index score: 3 vs 0-2	3.3 [2.4; 4.6]	<0.01	2.4 [1.7; 3.6]	<0.01	2.2 [1.5; 3.1]	<0.01
Antineoplastic treatment Chemotherapy+targeted therapy (TT) vs TT only Chemotherapy only vs TT only	2.1 [1.3; 3.6] 2.8 [1.5; 5.2]	0.01 0.01	2.2 [1.2; 3.9] 2.1 [1.2; 3.8]	0.012 0.015	1.6 [0.8; 3.2] 1.1 [0.6; 1.9]	0.17 0.84
History of VTE: Yes vs no	1.9 [1.3; 2.5]	<0.01	1.7 [1.2; 2.4]	<0.01	1.3 [0.9; 1.9]	0.10
Cancer stage: Metastatic vs local	1.6 [0.9; 2.7]	0.088	NI		2.3 [1.5; 3.5]	<0.01

NI: not included in the analysis.

Conclusions: In the absence of clear guidance, the use of thromboprophylaxis remains low and rather empiric even though the selection of LMWH by the majority of participants and treatment duration seems appropriate based on available data to date. ECOG index, metastatic malignancy, chemotherapy and history of thrombosis were significantly associated with the decision to use thromboprophylaxis in most situations.

Legal entity responsible for the study: Guy Meyer

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1563P Literature review of TPOR agonists for CIT

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Background: Chemotherapy-induced thrombocytopenia (CIT) can lead to dose delay/reduction. Currently there are no specific treatment recommendations beyond transfusion. We performed a systematic literature search on the use of thrombopoietin receptor (TPOR) agonists for CIT.

Methods: We searched the Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, PubMed, EMBASE, clinicaltrials.gov, and Health Technology Assessments from 1995-2017 for studies of TPOR agonists [eg, romiplostim, eltrombopag, TPO, and megakaryocyte growth and development factor (MGDF)] for CIT. Each publication was independently reviewed by two people and data extracted into Excel.

Results: We screened 892 titles/abstracts, assessed 52 articles, and abstracted data from 14 articles and 15 abstracts/posters from 1997-2016 (10 TPO, 7 MGDF, 8 romiplostim, and 4 eltrombopag), which included 18 randomized trials. TPOR agonist regimens varied widely. Common cancers included leukemia/lymphoma (n = 8 studies) and non-small cell lung cancer (n = 4), and common chemotherapies were platinum-based (n = 15) or included cytarabine (n = 5). Median or mean baseline platelet counts were 56×10^9/L-324×10^9/L in studies to treat CIT (N = 7) and 109×10^9/L-597×10^9/L in studies to prevent CIT (N = 22). The 16 placebo-controlled or crossover studies (MGDF n = 6 studies, TPO n = 5, romiplostim n = 3, eltrombopag n = 2) generally found that TPOR agonists increased platelet counts and reduced transfusions and dose delays/reductions (Table). Safety measures included thromboses (n = 19 studies) and bleeding (n = 8).

Table: 1563P Study Design and Endpoints TPOR Agonist vs. Control (Range study incidences)

CIT Prevention: Vs. Placebo/Observation or Crossover (n = 16 studies)	TPOR Agonist (N = 625)	Control (N = 428)
Efficacy Endpoint		
Chemotherapy dose delay/reduction	3% - 40%	58% - 75%
Grade 3-4 thrombocytopenia	0% - 100%	0% - 42%
Platelet transfusions	6% - 58%	8% - 83%
Safety Endpoint		
Thrombosis	0% - 29%	0% - 33%
Bleeding	0% - 100%	0% - 50%
CIT Treatment: Vs. rhIL-11 (n = 2 studies)	**TPOR Agonist (N = 63)**	**Control (N = 71)**
Efficacy Endpoint		
Chemotherapy dose delay/reduction	N/A	N/A
Grade 3-4 thrombocytopenia	Grade 3: 54% Grade 4: 14%	Grade 3: 85% Grade 4: 41%
Platelet transfusions	11%	30%
Safety Endpoint		
Thrombosis	N/A	N/A
Bleeding	N/A	N/A
CIT Treatment: Vs. PBO/Observation or Crossover (n = 2 studies)	**TPOR Agonist (N = 172)**	**Control (N = 65)**
Efficacy Endpoint		
Chemotherapy dose delay/reduction	N/A	N/A
Grade 3-4 thrombocytopenia	N/A	N/A
Platelet transfusions	N/A	N/A
Safety Endpoint		
Thrombosis	5% - 13%	7% - 21%
Bleeding	2% - 9%	9%

Conclusions: While TPOR agonists have not been approved for use in CIT, this literature review suggests that TPOR agonists may increase platelet counts and decrease chemotherapy dose delay/reduction. Further study with well-characterized bleeding and platelet thresholds is needed to explore the possible benefits of TPOR agonists for CIT compared with current care options (eg, transfusions, dose reduction).

Legal entity responsible for the study: Amgen Inc.

Funding: Amgen Inc.

Disclosure: G.A. Soff: Research support from Amgen. J. Fryzek: Employee of EpidStat, which serves as a consultant with Amgen. M. Mullins: Consultant for EpidStat, which itself consults for Amgen. L.C. Bylsma: Employee of EpidStat, which consults for Amgen. J.K. Park: Amgen employee. All other authors have declared no conflicts of interest.

1564P Random optimization interactive system based on Kernel learning (RISK) for venous thromboembolism risk assessment in chemotherapy-treated cancer patients

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Background: Using a combined approach of Kernel machine-learning (ML) and random optimization (RO) techniques we recently developed a set of predictors (ML-ROs) for VTE risk assessment. Aim of this study was to validate a model incorporating the two best ML-ROs to devise a web-based graphical interface for VTE risk stratification.

Methods: Pre-chemotherapy age, sex, tumor site and stage, hematological attributes, fasting blood lipids, glycemic indexes, liver and kidney function, BMI, ECOG, supportive and anti-cancer drugs of 608 cancer outpatients were entered in the model, with numerical attributes analyzed as continuous values. Variables were clustered into groups according to clinical significance, and RO was used to devise their relative weight in final prediction.

Results: VTE occurred in 7.1% of patients. Overall, 6% were at high-risk for VTE, as per current guidelines (Khorana Score (KS) $\geq$3), 11% of which had VTE during treatment. 42% and 52% were at intermediate (KS 1/2) or low-risk (KS = 0), with VTE rates of 9% and 5%, respectively. Accordingly, the performance of KS, despite a 94% specificity, was characterized by a 9% sensitivity with an area under the ROC curve (AUROC) of 0.589, translating into non-significant positive (+LR) [1.58 (0.48-4.30)] or negative likelihood ratio (-LR) [0.96 (0.83-1.04)]. Conversely, the VTE risk prediction performance of the combined ML model showed a 0.716 AUROC, which was significantly higher than that observed with KS (difference between areas: 0.127, $p = 0.0044$). At a criterion >1 (risk estimate achieved by both predictors) this combined approach showed significant +LR [2.30 (1.70-2.82)] and -LR [0.46 (0.28-0.69)] and a 4.9 Hazard Ratio (95%CI: 2.5-9.4) with a 6-month VTE rate of 3.4% in the low-risk, compared with 14.9% in the high-risk category.

Conclusions: These results demonstrate that a ML approach, optimizing the relative weight (by RO) of groups of clinical attributes, is of clinical value for VTE risk prediction, performing better than KS. We are now finalizing the architecture of a web service with a graphical interface helping oncologists in the critical phase of decision making.

Legal entity responsible for the study: RISK Research Group

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1565P Association between systemic inflammation and symptoms in advanced cancer patients

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Background: There is growing evidence relating inflammation as a prognostic factor in cancer patients. Previous reports have found a small but significant association between systemic inflammation and symptoms in advanced cancer patients. The aim of this study was to analyse the relationship between systemic inflammatory response markers with the symptoms and performance status of advanced cancer patients that have been admitted to an Acute Palliative Care Unit (PCU).

Methods: We conducted an observational study including all cancer patients admitted in the PCU between January 2012 and April 2015. We performed a correlation analysis (spearman's rho) between serum C-reactive-protein (CRP), the modified Glasgow Prognostic Score (mGPS) and Neutrophil-to Lymphocyte Ratio (NLR) with patients symptoms recorded as the Edmonton Symptom Assessment Sytem (ESAS) and performance status recorded as Eastern Cooperative Oncology Group (ECOG), Barthel Index and Palliative Performance Scale (PPS). All data were collected within the first two days of admission.

Results: Data of 951 patients were available. The median survival was 17 days. CRP was significantly correlated with ECOG (ρ:0.180, P:0.000), dyspnoea (ρ:0.079, p:0.019), fatigue (ρ:0.162, $p < 0.001$), anorexia (ρ: 0.103, p:0.002), somnolence (ρ:0.096, p.0.009), wellbeing (ρ:0.012, $p < 0.001$), Barthel (ρ:-0.178, $p < 0.001$) and PPS (ρ:0.173, $p < 0.001$). In relation to mGPS, a significant correlation was found with ECOG (0.116, p:0.001), fatigue (ρ:0.184, $p < 0.001$), anorexia (ρ:0.107, p.0.003), somnolence (ρ:0.080, p.037), Barthel (ρ:-0.127, $p < 0.001$) and PPS (ρ:-0.125, $p < 0.001$). Finally, NLR was significantly correlated with ECOG (ρ:0.112, p0.001), dyspnoea (ρ:0.117, $p < 0.001$), fatigue (ρ:0.107, p:0.002), Barthel (ρ:-0.115, $p < 0.001$) and PPS (ρ:-0.100, p:0.002).

Conclusions: There is a small but significant correlation between systemic inflammation and symptoms. Further studies are needed to confirm the results and to test this relation in earlier phases of the disease.

Legal entity responsible for the study: Hospital Universitario La Paz

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1566P Outcomes of patients with malignancy admitted to the intensive care units (ICU): A prospective study

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Background: Decisions regarding whether advanced cancer patients should be admitted to the intensive care units (ICU) is based on a complex suite of considerations, including short and long term prognosis, quality of life, and options to treat cancer. We set to describe demographic, clinical, and survival data and to identify factors associated with short and long term mortality in critically ill advanced cancer patients with non-elective admissions to general ICUs.

Methods: Critically ill adult cancer patients non-electively admitted to the ICUs at the American University of Beirut Medical Center (AUBMC) between August 2015 and 2016 were included. Demographic, clinical, and laboratory data was prospectively collected from first day of ICU admission up to 30 days after discharge. This study was observational and clinical decisions were left to the ICU team and attending physician.

Results: 91 patients were enrolled between August 2015 and 2016, with 41 patients (46%) dying in the ICU, and 12 patients (13.5%) within 30-days post-discharge. 7 patients were lost to follow-up. Mean OS was 137 days, and median OS was 31 days since date of admission to the ICU. Most common reasons for ICU admission were sepsis (68.5%) and respiratory failure (19%). Cox regression showed direct admission from the ED (2.4 times more likely to die), those with uncontrolled malignancies (1.8 times), chemotherapy within the last 30 days prior to ICU admission (2.3 times), and development of multi-organ failure (MOF) (2.5 times) in the ICU are major predictors of poor prognosis.

Conclusions: Our study showed receiving chemotherapy within thirty days prior to admission as a predictor of poor outcome in univariate and multivariate analyses. This has not been reported in a study population of this kind before. Also, many studies state that developing MOF, whether in the ICU or prior to admission negative prognostic factor. Finally, our study found that direct admission from the ED is a negative prognostic factor, which has only been reported for hematological malignancies in other studies. Thus, there is a need for the development of proper admission criteria for this population.

Legal entity responsible for the study: American Unviersity of Beirut Medical Center

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1568P Management of thrombosis in cancer patients in Greece

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Background: Venous thromboembolism (VTE) is a common cause of adverse outcomes in patients with cancer. The risk of VTE varies with cancer type, stage, grade, therapy and other patient characteristics. Low-molecular-weight heparin (LMWH) remains the standard therapy for VTE in cancer patients.

Methods: This is an observational study conducted by the Hellenic Society of Medical Oncologists (HeSMO) that aims to record and highlight the current clinical practice and management of VTE in patients with cancer in 18 Greek centers, with nationwide dispersion.

Results: The participating centers reported a total of approximately 4300 cancer patients managed on a monthly basis, where the vast majority (80%) were treated in an outpatient setting. For this study, 340 patients with active cancer were enrolled, with the following characteristics: 53,2% male; mean age 64,3; 62.1% of patients had PS of 0-1; tumor types: lung 22,3%, pancreas 16,3%, colon 13,6%, breast 11%, stomach 8,3%, ovarian 6,5% and other tumors 21,7%. The majority of patients (95,3%) received anticancer treatment; 21,3% were inpatients and 78,6% outpatients. Among these 340 patients, 86 were diagnosed with VTE: 81,4% had symptomatic VTE while 18,6% had incidental VTE. Regarding patients with VTE,94,2% received anticancer treatment and the majority of these (65,1%) were treated in an outpatient setting. Of the patients diagnosed with VTE, 76,9% had performance status 0-1 and 74,4% had metastatic disease. In the metastatic stage there was no differences in the incidence of symptomatic or incidental VTE, 75% vs 74,3% respectively ($p = 0,99$). Highest percentage of incidental VTE observed was in patients with lung cancer (43,8%), followed by pancreatic (18,8%) and colon cancer (12,5%). All patients with VTE received antithrombotic treatment with LMWH according to the current clinical guidelines.

Conclusions: The majority of patients who developed VTE were outpatients undergoing anticancer treatment with metastases. Incidental VTE was more frequent in patients with lung cancer. Our findings of 18,6% incidental VTE further confirm the previously described results in similar studies.

Legal entity responsible for the study: Hellenic Society of Medical Oncology (HeSMO)

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1569P Incidence and outcome of Incidental Pulmonary Embolism (IPE) in oncology patients with current macroscopic disease

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Background: IPE is defined as a PE detected on a CT scan (not a pulmonary angiogram) done for reasons other than suspected PE. This study is to evaluate the incidence of IPE in oncology patients with current macroscopic disease, and the outcome that could potentially be affected by a delay in starting anticoagulation therapy due to delayed reporting of these routine (non-urgent) scans.

Methods: CT thorax with iv contrast done on oncology patients between 01.01.15 – 31.12.15 in two district general hospitals in a cancer network were identified from the database. The scan reports and clinic letters were reviewed for data on cancer diagnosis, macroscopic disease, PE, treatments and survivals.

Results: 2147 scans were identified. 543 scans were excluded due to absence of macroscopic disease (No IPE was reported in any of these scans.) leaving 1604 scans eligible for this study. Incidence for different tumour is shown in the table 1. 26 IPE patients are female = 15; median age = 66 (range 32 – 90); main artery = 9; lobar artery = 5; average time from CT scan to anticoagulation (LMWH) therapy is 9.7 days (median = 5 days; range = 0 – 61 days; no treatment in 3 patients) mainly due to the delay in reporting (median = 1 day; range = 0 – 60 days). The median survival from the scan date is 7 months (range = 1 – 22) with 9 patients still alive and 2 lost to follow up. None of the patients whose anticoagulation started 5 or more days after the CT scan died within 3 months. IPE was absent in all subsequent CT scans. This happened without any anticoagulation therapy in one patient who had a segmental IPE. Table 1. Incidence of IPE for different tumour types

Table: 1569P

	Patients	Scans	Scans with IPE (% of total scans)
Lung	235	587	9 (1.5%)
Breast	148	267	5 (1.9%)
Colorectal	142	310	5 (1.6%)
Oeso/gastric	72	163	2 (1.2%)
Mesothelioma	8	19	1 (5.3%)
CUP	15	30	1 (3.3%)
Bladder	15	31	1 (3.2%)
NET	1	1	1 (100%)
Prostate	41	87	1 (1.2%)
Anal	1	2	0
Brain	1	1	0
H & N	8	18	0
Heptaobiliary	10	20	0
Melanoma	3	4	0
Ovary	3	4	0
Pancreas	26	58	0
Skin	2	0	0
Total	731	1604	26 (1.6%)

Conclusions: Incidence of IPE in oncology patients with current macroscopic disease is low (1.6%) in daily practice. Most patients are likely to have lung, breast and colorectal cancers. This is probably due to the fact that these are common tumours, and the frequency of scanning in their management. No sudden death or mortality within 30 days was noted among patients who had anticoagulation therapy started 5 or more days after the CT scan. Spontaneous resolution of PE happened in one patient with segmental PE. More research is needed to select patients who may not get any meaningful benefit from anticoagulation in the presence of advanced malignant disease.

Legal entity responsible for the study: Maung Maung Myat Moe

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1570P Immune related adverse events associated with ipilimumab and nivolumab

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Background: Immune related adverse events (IrAEs) are unique and completely different from what we have seen previously. There is no prospective data on these toxicities and guidelines are based on symptomatic management from the ongoing clinical trials. Ipilimumab and nivolumab induce irAEs to the skin, gastrointestinal, liver, endocrine and other systems.

Methods: A **retrospective** review of data from 45 patient records were used to describe the IrAE's associated with 19 patients treated with Ipilimumab and 25 patients treated with Nivolumab and 1 patient with combination of ipilimumab and nivolumab. This is a single centre review in an expanded access programme/clinical trial setting.

Results: A total of 45 patients (28 males, 17 females) were analyzed. The median age was 63 years. Three patients with metastatic melanoma, 18 with non-small cell lung cancer (NSCLC), 2 with renal cell carcinoma and 2 with Hodgkin's disease were treated with nivolumab and 19 with metastatic melanoma received ipilimumab. One patient with combination of ipilimumab and nivolumab. In total 167 cycles of nivolumab (median = 4, range 1-16) and 60 cycles of ipilimumab (median = 4 cycles, range 1-4) were administered. The patient receiving combination of ipilimumab and nivolumab received 1 cycle. Seven IrAEs are described in 15 ipilimumab treated patients. These include endocrinopathy in 3 patients (hypophysitis in patient and hyphothyroidsm in 2 patients), colitis in 3 patients (1 required infliximab) and hepatitis in 1 patient. Among the patients treated with nivolumab, 7 IrAEs were documented. These included pneumonitis in 2 patients, skin rash in 3 patients, mild diarrhea in 1 patient and mild uveitis in 1 patient. One patient developed autoimmune thrombocytopenia, and nephritis. Three chest infections were documented including pulmonary tuberculosis in a NSCLC patient. The patient receiving combination ipilimumab and nivolumab had grade 4 skin toxicity requiring treatment discontinuation. No IrAE related deaths were document.

Conclusions: A plethora of irAEs are described with anti-PD1 and anti-CTLA4 antibodies. Colitis was more common with ipilimumab while pneumonitis more common with nivolumab. Prompt IrAE's diagnosis will result in decreased morbidity and mortality.

Legal entity responsible for the study: BL Rapoport
Funding: None
Disclosure: B. Rapoport: MSD, BMS and Roche Speaker Engagements, Advisory Board and Contract Research All other authors have declared no conflicts of interest.

1571P Febrile Neutropenia: a systematic review of the first 5 years of a cancer unit

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Background: Febrile Neutropenia (FN) is a potentially life-threatening and dose-limiting complication of myelosuppressive chemotherapy (CT) that often requires hospital admission (HA). Patients (pts) with FN must initiate antibiotic (atb) therapy promptly and delay in diagnosis and subsequent treatment are associated with higher mobility and mortality.

Methods: Retrospective single institution review of all FN episodes that occurred in the years 2012 to 2016 in pts with solid tumors with an absolute neutrophil count (ANC) <1.000/µl and blood cultures (BC) collected within 30 days of an IV CT treatment. With a population base of 278.000 individuals, and 550 new solid tumor pts in Medical Oncology per year, we reviewed all BC collected during the first 5 years of Hospital Beatriz Angelo (2012-2016) and crossed with the registry of pts treated with IV CT. FN was defined as a tympanic temperature > 38 °C and ANC <1.000/µl and expected to decrease to < 500/µl in the following 7 days. Pts with hematologic malignancies were excluded.

Results: Among 1.947 eligible pts, 152 had a NF (8%) with a total of 173 NF episodes. Median age was 67yo; 90 were males (59%). Median initial ANC was 310/µl, range 20-990 (<500/µl in 69% and <100/µl in 17%). In the emergency room, median time from hospital nurse triage to medical observation (MO) was 38 min (range 4min-6h11m), MO to blood count specimen withdrawal 55min (range 10min-6h43m) and MO to arrival of BC to the lab 5h51min (range 24min-23h41m). 33 NF episodes were associated with positive BC (19%, 6 with two agents), 11 BC with Gram positive and 28 with Gram negative bacteria. 157 episodes led to HA (90%), 15 were treated as outpatients and in 1 NF episode the pt died at presentation from E. coli pneumonia. Median days of hospitalization was 8 (range 0-36). Median time on atb was 9 days (range 1-31), with first-line regimen including piperacilin/tazobactam in 110, amoxicilin/clavulanic acid + ciprofloxacin in 17, meropenem in 9, other agents in 11 and 1 with no treatment. Mortality during the NF episode was 20% (n = 34) from 173 NF episodes.

Conclusions: FN is a serious and common complication of CT treatment which must be diagnosed and treated rapidly. Delays in the evaluation of febrile cancer pts on systemic treatment may compromise the outcome of these pts.

Legal entity responsible for the study: João Moreira Pinto
Funding: None
Disclosure: All authors have declared no conflicts of interest.

1572P G-CSF and G-CSF biosimilars: a meta-analysis of randomized clinical trials in breast cancer patients

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Background: The granulocyte colony-stimulating factors (G-CSFs) filgrastim and pegfilgrastim are widely used to prevent neutropenia in cancer patients undergoing myelosuppressive chemotherapy. Several G-CSF biosimilars are available, their development involving a step-wise approach including analytical comparison with the reference and iterative process development. Randomized clinical trials (RCTs) have confirmed that the reference product and its biosimilar provide the same clinical efficacy and safety and play pivotal role in the totality of evidence concept. However some heterogeneity exists among the studies. For G-CSF biosimilars, patients with breast cancer (BC) are the most sensitive population in which to confirm similarity. The aim of this meta-analysis was to compare the clinical efficacy of approved or proposed G-CSF biosimilars (filgrastim or pegfilgrastim) with reference G-CSF in patients with BC.

Methods: A Medline literature search up to March 2017 identified randomized clinical trials (RCTs) comparing biosimilar G-CSF to reference in BC patients. Primary efficacy endpoint was mean difference in duration of severe neutropenia (DSN). Secondary efficacy measures were differences in depth of absolute neutrophil count (ANC) nadir and time to ANC recovery. Random effect models were fitted to obtain pooled estimates of the mean difference and their corresponding 95% confidence intervals (CIs).

Results: Eight eligible RCTs were included. Overall difference in DSN between reference and biosimilar medicines was not statistically significant (0.06 days [95% CI -0.05, 0.17]) (Table). The secondary efficacy endpoints also showed no significant differences between reference and biosimilars.

Conclusions: This meta-analysis showed no differences in clinical efficacy between biosimilar and reference G-CSF in breast cancer patients.

Legal entity responsible for the study: n/a
Funding: None
Disclosure: A. Krendyukov: Employee of Hexal AG G. Curigliano: Honoraria from Pfizer, Roche, Sandoz. All other authors have declared no conflicts of interest.

1573P Pharmacokinetic and pharmacodynamic comparability of B12019: A proposed pegfilgrastim biosimilar

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Background: B12019 is being developed as a biosimilar to Neulasta® (INN pegfilgrastim), a pegylated, long-acting form of recombinant human granulocyte-colony stimulating factor (G-CSF) for the prevention of chemotherapy-induced neutropenia. A clinical development program was conducted with B12019 in comparison to EU-authorised Neulasta to confirm the biosimilarity as established by analytical, functional and preclinical data.

Methods: The clinical development program for B12019 consisted of two clinical studies. Study B12019-101 investigated pharmacokinetics (PK) and pharmacodynamics (PD) comparability of B12019 to Neulasta. The 6mg single-dose, randomised, double-blind, two-way crossover study enrolled 172 healthy volunteers. The primary PK endpoints were the area under the plasma concentration-time curve ($AUC_{0\text{-last}}$) and the maximum concentration (C_{max}) as well as the area under the effect curve ($AUEC_{0\text{-last}}$) for absolute neutrophil count (ANC) for PD. In study B12019-102 immunogenicity and PD comparability of B12019 and Neulasta were investigated in a 3mg multiple-dose, randomised, double-blind, three-period, two-sequences crossover study in 96 healthy volunteers. Primary endpoints were $AUEC_{0\text{-last}}$ for PD and anti-drug antibody rate (ADA) for immunogenicity.

Results: Study B12019-101, using 6 mg, confirmed PK and PD comparability (compare also *Roth et al, Blood, Dec 2016*). In study B12019-102, 82 subjects were included in the model-based PD comparison. PD comparability was demonstrated, with the $AUEC_{0\text{-last}}$ geometric mean ratio with a CI of 99.6; 103.6 being within the pre-specified acceptance range. In both studies, no imbalance of ADA-positive samples after single or repeated dosing were observed. Neither anti-G-CSF nor neutralising antibodies were detected for B12019 or Neulasta.

Table: 1572P Mean and mean difference on duration of severe neutropenia* during chemotherapy Cycle 1

			Biosimilars		Reference products			Mean difference
Study and year of publication	Reference G-CSF	Biosimilar G-CSF	Mean	No. of patients	Mean	No. of patients	Weight	IV, Random, 95% CI
Blackwell 2015	Filgrastim	Filgrastim	1.17	107	1.2	107	14.2%	−0.03 [-0.32, 0.26]
Blackwell 2016	Pegfilgrastim	Pegfilgrastim	1.36	155	1.19	153	20.2%	0.17 [-0.07, 0.41]
Del Giglio 2008	Filgrastim	Filgrastim	1.1	140	1.1	136	6.4%	0.00 [-0.43, 0.43]
Harbeck 2016	Pegfilgrastim	Pegfilgrastim	0.75	155	0.83	155	28.1%	−0.08 [-0.28, 0.12]
Park 2016	Filgrastim	Pegfilgrastim	2.28	36	2.08	38	5.6%	0.20 [-0.26, 0.66]
Waller 2010	Filgrastim	Filgrastim	1.6	165	1.3	85	13.4%	0.30 [0.01, 0.59]
Waller 2016	Pegfilgrastim	Pegfilgrastim	1.2	127	1.2	67	12.2%	0.00 [-0.31, 0.31]
Pooled estimate (95% CI)				**885**		**741**	**100%**	**0.06 [-0.05, 0.17]**

Heterogeneity:$Chi^2 = 6.27$ ($P = 0.39$); $I^2 = 4\%$ *Days with absolute neutrophil count less than 0.5×10^9/L (<500/μL)

Conclusions: · The clinical program confirmed the biosimilarity of B12019 and Neulasta in highly sensitive clinical study settings. · PK comparability of B12019 and Neulasta was demonstrated at the clinical dose of 6 mg. · PD comparability of B12019 and Neulasta was shown at the clinical dose of 6 mg and the reduced dose of 3 mg. · The safety and immunogenicity profile of B12019 did not show any clinically meaningful differences to Neulasta.

Clinical trial identification: NCT02912377 NCT02629562

Legal entity responsible for the study: Cinfa Biotech S.L., Olloki, Spain

Funding: Cinfa Biotech S.L., Olloki, Spain

Disclosure: K. Roth, H. Wessels, R. Jankowsky: Employee of Cinfa Biotech J. Hoefler: Employee of Staburo GmbH, statistical consultancy

1574P Efficacy and safety of RGB-02, a proposed biosimilar pegfilgrastim to prevent chemotherapy-induced neutropenia: Results of a randomized, double-blind, phase III clinical study vs. reference pegfilgrastim in patients with breast cancer receiving docetaxel/doxorubicin

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Background: Treatment with recombinant human granulocyte-colony stimulating factor (G-CSF) is 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 pegfilgrastim product Neulasta®. Here we are presenting the results of a randomized, comparative, double-blind, multicenter study to evaluate efficacy and safety of RGB-02 in breast cancer patients receiving cytotoxic regimen (EudraCT nr: 2013-003166-14).

Methods: 239 women presenting with breast cancer were randomized to RGB-02 (n = 121) and to the reference pegfilgrastim, Neulasta® (n = 118). All patients received up to 6 cycles of docetaxel/doxorubicin and a once-per-cycle injection of a fixed 6 mg dose of pegfilgrastim. Primary endpoint was the duration of severe neutropenia (ANC $< 0.5 \times 10^9$/L) in Cycle 1 (2-sided CI interval 95%). Secondary endpoints included incidence and duration of severe neutropenia, incidence of febrile neutropenia, time to ANC recovery, depth of ANC nadir, and safety outcomes.

Results: The mean duration of severe neutropenia in Cycle 1 was 1.7 (RGB-02) and 1.6 days (reference), with a difference (LS Mean) of 0.1 days (95% CI -0.2, 0.4). Therapeutic equivalence could be established as the CI for the difference in LS Mean lay entirely within the pre-defined range of ± 1 day. The incidence of severe neutropenia decreased from cycle 1 to 2 in both groups with no statistical significant differences, for RGB-02 from 84.6% (99 patients) to 54.1% (60 patients) and from 77.0% (87 patients) to 43.7% (45 patients) in the comparator group. Both groups were similar regarding mean time to ANC recovery with 3.4 ± 1.84 days (RGB-02) and 3.7 ± 1.88 days (reference) during Cycle 1. Safety profiles were comparable between groups.

Conclusions: Therapeutic equivalence and similar safety profiles between RGB-02 and Neulasta® as once-per-cycle administration could be demonstrated. RGB-02 can provide a biosimilar alternative for the prevention of neutropenia.

Clinical trial identification: EudraCT nr: 2013-003166-14

Legal entity responsible for the study: Gedeon Richter Plc.

Funding: Gedeon Richter Plc.

Disclosure: K. Horvat-Karajz, A. Illes: Employee of Gedeon Richter Plc. All other authors have declared no conflicts of interest.

1575P Impact of resistance exercise on metabolic syndrome (MetS) parameters in men receiving androgen deprivation therapy (ADT) for prostate cancer

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Background: Cardiovascular disease is the leading cause of death in men with prostate cancer. ADT is effective treatment, but can adversely impact MetS components, which may contribute to excess cardiac risk. We tested whether a resistance exercise program, designed to increase skeletal muscle mass during ADT, could offset adverse changes.

Methods: Prostate cancer patients on ADT were randomized to exercise (EX) or no exercise (noEX). EX was supervised, periodized resistance training followed by stretching 3x/week for 12 weeks, 45 min/session. noEX did home-based stretching 3x/week. Baseline and post-intervention measurements included weight, waist circumference (wCirc), lean body mass, lipids, insulin, glucose. Mean differences in changes were compared with intent-to-treat linear regression models adjusted for baseline values. Cohen's D effect sizes were calculated for these pilot data to estimate effects for a fully powered trial.

Results: Thirty-two men (EX n = 13, noEX n = 19) completed the protocol. Age (mean ± SD) was 67.3 ± 8.7 yr (range 52 - 84). Mean duration ADT was 14.4 ± 13.4 months (range 3 – 57). EX patients had higher baseline BMI with 63% >25 kg/m2 compared to 25% in the NoEX group, p = 0.024. wCirc decreased significantly (p = 0.032) in EX (-1.18 cm 95%CI [-3.3, -1.0] cm) compared to NoEX (+1.97 cm [0.2, 3.7]). Lean mass increased and body fat decreased in EX compared to NoEX. Moderate effect sizes (D = 0.2-0.5) were seen between groups for other parameters (see Table).

Conclusions: Supervised resistance exercise for 12 weeks improves wCirc and body composition in men receiving ADT for prostate cancer with moderate effect on other MetS parameters.

Clinical trial identification: NCT01909440

Legal entity responsible for the study: University of Southern California, Keck School of Medicine

Funding: National Strength and Conditioning Association, California State University Chancellor's Doctoral Incentive Program

Disclosure: All authors have declared no conflicts of interest.

1576P Body mass index (BMI), lifestyle behaviors, and perceptions in cancer survivors

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Background: Obesity is associated with poorer outcomes across multiple cancer types. Lifestyle behaviours (smoking, physical activity (PA) and alcohol) can improve outcomes among cancer survivors.

Methods: Cancer patients of all subtypes were cross-sectionally surveyed on their smoking, alcohol and PA levels, and their perceptions of these behaviours on quality of

Table: 1575P

	Baseline mean	Week 12 mean	Mean change [95% CI]	p	D
wCirc (cm) EX NoEX	106.8 97.9	105.9 99.6	−1.18 [-3.3, -1.0] 1.97 [0.2, 3.7]	0.032	0.8
Lean Body Mass (kg) EX NoEX	48.5 kg 51.5 kg	43.2 kg 48.6 kg	1.07 [0.35, 1.79] 0.09 [-0.5, 0.68]	0.047	0.8
Body Fat EX NoEX	36.8% 33.9%	35.9% 34.5%	−0.9 [-1.78, -0.01] 0.49 [-0.24, 1.22]	0.022	1
Diastolic BP (mmHg) EX NoEX	76.9 79.0	75.4 79	−1.91 [-6.3, 2.5] 0.31 [-3.3, 4.0]	0.437	0.3
HDL-C (mg/dL) EX NoEX	46.5 61.3	49.0 61.5	3.83 [-1.9, 9.6] -0.32 [-4.8, 4.1]	0.270	0.4
HOMA-IR EX NoEX	2.56 1.34	1.42 1.82	−0.63 [-1.9, 0.6] -0.01 [-1.0, 1.0]	0.433	0.3

life (QoL), fatigue and survival (OS). Multivariable logistic regression models evaluated the association of BMI 1 year prior to diagnosis with behaviour changes and perceptions.

Results: Of 1269 patients, 205 smoked at diagnosis and 44% quit at 1 year; 350 (at diagnosis) and 238 (at follow-up) met PA guidelines; 661 drank alcohol at diagnosis while 50% reduced consumption after. Median BMI was 25.8 (22% obese); 75%+ patients perceived PA as improving QoL and OS, while 70%+ described smoking and 55%+ described alcohol as worsening QoL and OS. At diagnosis, increased BMI was associated with ex-smoking (vs current smoking; P = 0.003), never using alcohol (vs former use; P = 0.05) and not meeting PA guidelines (P = 0.01). Among smokers at diagnosis, increased BMI was associated with smoking cessation (aOR = 1.08 per 1 unit BMI, P = 0.03) and perceptions that smoking worsens OS (aOR = 1.10, P = 0.04) and fatigue (aOR = 1.08, P = 0.08). Among those not meeting PA guidelines at diagnosis, increased BMI was associated with perceptions that PA worsens fatigue (OR = 1.02, P = 0.06) and is unsafe (OR = 1.04, P = 0.06), but were not associated with PA levels changes after diagnosis. Among drinkers at diagnosis, increased BMI was associated with perceiving alcohol to be less harmful (aOR = 0.93, P = 0.002) and less likely to worsen OS (aOR = 0.96, P = 0.04) and fatigue (aOR = 0.97, P = 0.09), but not with alcohol use changes after diagnosis. BMI was not associated with counselling rates; however, 66% of current smokers received cessation counselling while only 14% of current drinkers and 13% of those not meeting PA guidelines received counselling on their respective behaviours.

Conclusions: Obese patients were more likely to quit smoking and perceive it to be harmful but less likely to perceive alcohol as harmful. Survivorship programs should consider focusing on PA and alcohol counselling in obese patients.

Legal entity responsible for the study: Princess Margaret Cancer Centre

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1577P Barriers to improving awareness of the importance on exercise and dietary intervention, impact of it on lung cancer survivors' behavior

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Background: Awareness of the importance on exercise and dietary intervention can provide significant benefits for lung cancer patients and survivors. This study first aimed to identify the barriers and preferences to improving awareness of the importance on exercise and dietary education. In addition, the study also explored the impact of patients' awareness of the importance on exercise and diet education toward the stage of behavior change, intention of actual participation to the programs.

Methods: Total 830 lung cancer survivors from two hospitals in South Korea participated in this postal questionnaire–survey. Standardized measures including patients' socio-demographic variables, preferences for appropriate education time and place were identified as the barriers for their awareness of the importance of exercise and diet counseling program. In addition, the impacts of it on each intention of actual participation to both programs and maintaining regular exercise and balanced diet were analyzed in order.

Results: Patients who recognized exercise education program very important had more intention of actual participation to the program (adjusted Odds Ratio [aOR], 2.11; 95% Confidential Interval [CI], 1.57-2.83). In addition, subjects who recognized diet counseling programs very important maintained their behavior of balanced diet more than 6 months (aOR, 2.57; 95% CI, 1.92-3.61). However, significant differences based on the socio-demographic variables and program preferences (i.e., lower education and income, preferred time and place etc.) were identified as main barriers for survivors' awareness of the importance of the exercise and diet counseling program.

Conclusions: Identification of main barriers provides valuable information regarding improving survivors' awareness of the importance on exercise and dietary intervention, which should be targeted in maintaining future physical activity and balanced diet, and encouraging the intention of actual engagement to the programs.

Legal entity responsible for the study: Ministry of Health & Welfare, Republic of Korea

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1578P Current perspectives of healthcare providers on weight loss and supportive nutritional care in cancer patients

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Background: Malnutrition and cachexia occur in most cancer patients (pts) impacting quality of life (QoL) and anticancer treatment (Tx) outcomes. Nutritional care can help reverse weight loss and improve pt outcomes; however, previous surveys at ESMO (2014, 2015) suggest nutritional care/assessment is insufficiently implemented in clinical practice, despite educational and academic efforts.

Methods: This survey created by the authors, including questions from prior surveys, was completed by ESMO 2016 delegates visiting the Nutricia booth.

Results: Of 2,011 respondents, 78% were medical oncologists, 56% were Europe based; 61% always discuss nutritional aspects during multidisciplinary tumor boards. To assess malnutrition, 44% measure weight, 30% evaluate systemic inflammation, and 14% assess muscle loss. Eligibility of pts to receive nutritional support is assessed before (48% [44% in 2015; 47% in 2014]) or during (54%) initiation of anticancer Tx, at primary diagnosis (28%), if weight loss is visible during outpatient visits (42%), and when anticancer Tx ends (26%). Main impacts of malnutrition are increased anticancer Tx toxicity (58%; 2015: 53%; 2014: 53%), surgery/radiotherapy complications (40%; 37%; 36%), anticancer Tx discontinuation/decreased effectivity (54%; 40%; 40%), decreased QoL (58%; 56%; 54%), impaired physical function (47%; 44%; 45%), or distress of family members (35%; 32%; 32%). Main goals of nutritional support include QoL (65%; 69%; 64%), completion of anticancer Tx (54%; 52%; 45%), or stabilizing weight (48%; 44%; 47%). Popular approaches to minimize weight loss are antiemetics (48%; 56%), appetite stimulants (41%; 48%), more-effective anticancer Tx (39%; 47%), anticachexia drugs (38%; 43%), and timely and individually tailored dietary advice (36%). During systemic Tx, 85% apply physical exercise programs (either alone or in combination with nutritional care).

Conclusions: Compared with our previous surveys, awareness and assessment of malnutrition in cancer pts seems slightly increased. HCPs recognize impacts of malnutrition but may need better guidance on how to improve nutritional care in the supportive and palliative setting.

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1579P A survey of patient acceptance of skin toxicities from cetuximab-based therapy

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Background: Inhibition of the epidermal growth factor receptor (EGFR) extends patient survival in multiple tumor types. However, EGFR inhibition is associated with skin toxicities such as mild to moderate acneiform rash, which can be severe in up to 18% of patients. A previously performed structured literature search revealed an unmet need for research regarding the influence of dermatologic adverse events (dAEs) on patients' quality of life (QoL), patient acceptance of cancer treatments, and therapeutic risk/benefit tradeoff from the patients' perspective. This survey reports on these topics in patients who received the anti-EGFR monoclonal antibody cetuximab.

Methods: Using a multinational survey that included 195 patients, we conducted a subanalysis of 66 patients who previously received cetuximab-based cancer therapy (44 with metastatic colorectal cancer [mCRC] and 22 with squamous cell carcinoma of the head and neck [SCCHN]) to gauge attitudes regarding skin toxicities.

Results: 64/66 patients (43/44 with mCRC and 21/22 with SCCHN) experienced dAEs. Skin toxicities were cited as causing pain and physical discomfort as well as impairing QoL. Despite the negative social, physical, and functional impacts of dAEs, 70% of patients with mCRC and 64% of patients with SCCHN who received cetuximab stated that they would prefer a more efficacious cancer therapy that induced more severe skin reactions over a less efficacious therapy associated with less severe skin reactions. Furthermore, in an efficacy-safety tradeoff exercise, nearly two-thirds of patients (65%) stated that they would accept a new therapy with improved efficacy, even if 1 out of every 2 patients experienced a severe skin rash on this therapy.

Conclusions: Patients with mCRC or SCCHN who previously received the anti-EGFR antibody cetuximab as part of their cancer therapy were willing to accept skin toxicities as an AE if these toxicities were the anticipated byproduct of a more effective therapeutic regimen.

Legal entity responsible for the study: Merck KGaA, Darmstadt, Germany

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1580P Increase in cetuximab-induced skin rash and hypomagnesemia in patients receiving concomitant treatment with proton pump inhibitors (PPIs): A possible drug interaction?

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Background: Proton pump inhibitors (PPIs) may interact with several orally administered drugs, possibly by raising gastric pH levels, leading to altered dissolution and absorption. In a previous study, we found that co-administration of PPIs with cetuximab was associated with increased skin toxicity. To confirm this preliminary observation, we tested this observation retrospectively. Since both these drugs can induce hypomagnesemia, the possibility of synergism between them was also tested.

Methods: The files of patients with metastatic colorectal carcinoma (mCRC) or head and neck (H&N) carcinoma treated at our center with cetuximab as a single agent or in combination with chemotherapy or radiotherapy were reviewed. All eligible patients treated with cetuximab during 2015 and 2016 were included in the study. The concomitant use of PPIs was defined if a drug belonging to that class was included in the patient's chronic medications list.

Results: One hundred eighteen patients (61 with H&N carcinoma, 57 with mCRC) were included in the study. Median follow-up from onset of cetuximab was 12.6 months [range, 0.5-63.2 months]. Fifty-eight patients received PPIs concomitantly with cetuximab. Skin toxicity of any grade was reported in 33/58 (56.9%) patients on PPIs compared with 22/60 (36.7%) patients not on PPIs ($p = 0.08$). Grade 3-4 skin toxicity was reported in 19/58 (32.8%) patients on PPIs compared to 2/60 (3.3%) not on PPIs ($p = 0.001$). Median time to detection of severe skin toxicity was 0.7 months [range, 0.2-11.0 months]. Hypomagnesemia (Mg serum level <1.2 mg/dL) was reported in 14/58 (25.9%) PPIs treated patients compared with 5/60 (10.4%) patients not on PPIs as a chronic medication ($p = 0.08$). Median time to detection of hypomagnesemia was three months [range, 0.4-52.8 months]. Complications of all grade skin toxicity or hypomagnesemia were reported in 40/58 (69%) patients on PPI compared to 23/60 (38.3%) patients not on PPIs ($p = 0.04$). Grade 3-4 skin toxicity or hypomagnesemia (Mg < 0.9mg/dL) were reported in 23/58 (39.7%) patients on concomitant treatment with PPIs compared with 3/60 (5%) patients not on PPIs ($p = 0.001$).

Conclusions: Both the rate and the severity of cetuximab-induced skin toxicity and hypomagnesemia were increased by chronic concomitant administration of PPIs. A prospective study is needed to confirm the possible interaction between cetuximab and PPIs.

Legal entity responsible for the study: Mahmoud Abu Amna
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1582P NeuroCog-FX study: A multicenter cohort study on cognitive dysfunction in patients with early breast cancer

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Background: Many breast cancer patients complain about cognitive dysfunction (CD) with mnestic and attentional deficits. These complaints persist even after completion of therapy in approximately one third of the patients and affects both social life and working capacity. The exact nature and genesis of CD in breast cancer patients is still not fully understood and risk factors are not yet described.

Methods: To determine CD and risk factors, we used the computer-based neuropsychological test NeuroCog-FX during a three weeks oncological rehabilitation in breast cancer patients. Eight subtests addressed attention, working memory, verbal and figural memory, and language. Test duration was <30 minutes. A cognitive deficit was diagnosed if at least one subtest was clearly below average (score < M - 1.5 SD) of the normative age group. The data on cognitive function were correlated with the level of depression (PHQ-9 test), QoL (EORTC QLQ-30) and clinical parameters (nodal status, chemo-/radiotherapy and endocrine therapy).

Results: From February 2013 to December 2014 a total of 476 patients were recruited in 9 oncological rehabilitation centers in Germany. NeuroCog-FX was used to examine 439 patients. Median age was 50 years (range: 24-62 years); 93% of patients had early tumor stage (T0-T2) and 67% were node-negative. Sixty-one percent of the patients received chemotherapy while 84% of the subjects underwent radiotherapy. CD was found in 59% and a moderate to severe depression in 38% of the patients. The severity of depression was correlated with slower reaction times and reduced verbal memory performance. These two cognitive parameters were also associated with a reduced global health status and a reduced physical function score on the EORTC-QLQ30 questionnaire suggesting an impact of cognitive deficits on quality of life. Cognitive function was not associated with type of treatment or node status.

Conclusions: In this large and homogeneous cohort of breast cancer patients, CD has been shown in most of the subjects using a valid test method. CD was associated with depression and reduced quality of life. Neither tumor therapy nor other clinical parameters had a significant impact on development of CD.

Legal entity responsible for the study: Frankfurt
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1583P Autonomic neuropathy in geriatric patients with gynecologic cancer receiving taxanes and platinum chemotherapy

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Background: The standard of care for ovarian cancer in elderly is using paclitaxel and carboplatin, an effective and efficient combination, but has serious toxicities. Peripheral neurotoxicity is one of the commonest toxicities which are seen occurring in 60% to 90% of patients. It is debilitating and vexing. Unfortunately, there is very little or no data regarding autonomic neuropathy in this setting. This study is an attempt to highlight this problem.

Methods: Single center cohort study of patients for the period 2013-2015. All patients were above the age of 65 years. 88 patients were tested for. All patients were screened for neuropathy using standard forms and methods including positional sense and stereognostic sense for neuropathy. NCI scales of grading peripheral neuropathy were followed. Autonomic neuropathy assessments were done by cardio vascular autonomic reflex test and gastro-intestinal autonomic neuropathy by using gastric phase emptying test. Genito-urinary autonomic neuropathy was tested for erectile dysfunction and bladder dysfunction. The tests were administered at baseline after 2nd, 4th and 6th cycle or if the patient complained of suggestive symptoms.

Results: 37% of patients developed grade 3/4 peripheral neuropathy. 59% of patients developed symptomatic autonomic neuropathy. Cardio vascular autonomic neuropathy occurred in 30% while gastric neuropathy was seen in 19%. Combined was seen in 10%. Constipation, diarrhoea and reeling of head were the most common complaints. Autonomic neuropathy was more common in diabetics 60% vs 48% ($p > 0.05$). Attempts to intervene using pharmacotherapy methods and non-pharmacotherapy methods were attempted.

Conclusions: Autonomic neuropathy seems to be common in geriatric population treated by this drug combination although there is not much mention either in real life or in clinical trials or if available as data attributed to other causes. Caution must be exerted in patients in diabetics and proper screening should be done in this patient population for autonomic neuropathy and peripheral neuropathy.

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Disclosure: All authors have declared no conflicts of interest.

1586P Potential drug interactions in older patients with cancer: Updated data from the ELCAPA cohort survey

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Background: Because of polypharmacy, older cancer patients are at risk of adverse events related to potential drug interactions (PDI). We aim to identify PDI in daily medications, between daily medications and chemotherapy (CT), and related potential clinical outcomes (PCO).

Methods: All cancer patients aged ≥70 years, referred for geriatric assessment at Henri Mondor Hospital (Paris' area, Créteil, France), included in the prospective ELCAPA cohort survey (2007–2014), and who received CT were included. PDI were identified using Lexicomp® (LexiComp, Hudson, USA) software and the Theriaque® website. PDI were classified as: A, no interactions; B, no action needed; C, monitor therapy; D, consider therapy modification; X, avoid combination. Factors associated with grade C or D/X PDI were analyzed using ordered multivariate logistic regression.

Results: We analyzed 442 patients (median age: 78 years; 49% women). Main tumor sites were upper digestive tract (23%), colorectal (21%), urological tract (19%), lymphoid malignancies (15%), and breast (12%); 23% had metastasis. Median number of drugs/patients/day was 3 (Q1-Q3 [1-6]). We identified 1742 PDI: 87% in daily medications (183 patients had grade C PDI (41%), 128 grade D/X (29%)), and 13% between daily medications and CT (66 patients had grade C PDI (15%), 56 grade D/X PDI (13%)). Main PCO involving daily medications were hypotension risk (33%), psychotropic effects (17%), glycemic (12%) and hemostasis (9%) dysregulations. Main PCO related to PDI involving CT were risk of CT over-exposure (34%), hypotension risk (20%), and hemostasis dysregulation (11%). In multivariable analysis, adjusted for

number of drugs, factors associated with grade D/X PDI, both with or without CT were: ≥2 metastatic sites ($p = 0.01$) and lymphoid malignancies ($p = 0.01$). Patients living alone had less grade D/X PDI in daily medications ($p = 0.003$), while breast cancer ($p = 0.04$) was associated with more grade D/X PDI in daily medications. Higher body mass index was associated with grade D/X PDI involving CT ($p = 0.03$).

Conclusions: The high prevalence of PDI in older cancer patients highlights the need to assess precisely the iatrogenic risk before anti-cancer treatment.

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1587P How do Spanish medical oncologists manage breakthrough pain? A national study

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Background: Many cancer patients experience transient exacerbations of severe pain, known as breakthroughcancer pain (BTcP), a complex pain state that negatively impacts patients' quality of life. We evaluated the knowledge of BTcP management according to the Spanish Society of Medical Oncology (SEOM) clinical practice guideline.

Methods: Fundación ECO (Foundation for Excellence and Quality in Oncology) conducted a survey regarding knowledge of managing BTcP focusing on: awareness of SEOM guidelines, agreement with recommendations, and implementation in clinical practice.

Results: A total of 83 oncologists responded: 65% were female, mean age was 40-year-old and mean time in practice was 13 years. Overall, 82% were aware of guidelines and the agreement with recommendations ranged from 99-100%. Regarding implementation, 87.6% declared full compliance, nonetheless adherence in clinical practice ranged from 30.1% to 86.7% for documentation of BTcP episodes in medical records, and 75.9% to 91.6% for therapeutic management.100% of oncologists agreed on the prescription of specific medication for BTcP and most of them (91.6%) that rapid onset fentanyl formulations should be considered the first line of treatment.

Conclusions: Our results support efforts and targeted education of medical oncologists in BTcP management. However, our study raises concerns about guidelines dissemination deficiencies as well as vague statements that underscore a need for more effective dissemination policy and more effective detailed recommendations.

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1588P Enhanced supportive care in early phase clinical trials

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Background: Enhanced Supportive Care (ESC) is a fresh approach to supporting patients through cancer treatment and recognised nationally by NHS England. The Supportive Care Team (SCT) and Experimental Cancer Medicine Team (ECMT) at the Christie Hospital applied the validated 'Integrated Palliative care Outcome Scale' (IPOS; http://pos-pal.org/) in a pilot study examining the impact of ESC for patients (pts) entering early phase clinical trials. The main aims of this study were to maximise patient recruitment and retention and enhance the patient experience within the context of experimental cancer medicine clinical trials.

Methods: The IPOS tool was used to assess the effect of ESC on patient outcomes in pts on an ECMT trial. It was administered by the SCT healthcare professionals to any pts with baseline symptoms thought to be related to their underlying cancer diagnosis and at all pt visits as per trial protocol. Analysis is based on patient data where both an initial and subsequent form had been completed. Three aspects of the IPOS tool were reviewed; the overall IPOS score, the score for all symptoms as a whole and individual pain score.

Results: Data was collected from 24 pts within ECMT trials during a four-month period in 2016. The mean age was 56 years (31 to 79); 10 male and 14 female. Performance status at initial assessment was 0 (3 pts); 1 (18 pts); 2 (1 pt); unknown (2 pts). 16 pts had no previous contact with SCT services. The commonest reason for referral to the SCT was for optimisation of pain control (24/24 pts) followed by general symptom control (8/24) and psychological issues (2/24). 21 pts were seen on the day of referral, 3 pts seen ≤ 8 days of referral. 16/24 pts (67%) reported improvement in pain (and IPOS scores) within 4 weeks and 17/24 pts (71%) reported improvement in overall symptom control within 4 weeks.

Conclusions: This study has demonstrated the effectiveness of ESC on the outcomes of patients being reviewed by the SCT on ECMT clinical trials. There were considerable reductions in the overall IPOS scores and in pain score specifically. ESC has now been adopted into routine practice by our ECMT, and we are the first unit to do so in the UK. We next plan to measure the impact of ESC on patient experience, adverse events on trials, hospital admissions and treatment duration.

Legal entity responsible for the study: Experimental Cancer Medicine and Enhanced Supportive Care Team

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1589P Cancer patient interest and perceptions of lifestyle behavior programs

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Background: Lifestyle behaviors including smoking cessation, physical activity (PA) and alcohol moderation are important aspects of a cancer survivorship program. We assessed cancer patient (pt) interest and perceptions of programs for these behaviours.

Table: 1587P

CPG AWARENESS 81.93% (68/83)	AGREEMENT	IMPLEMENTATION (in medical records)	IMPLEMENTATION (ranked drug of choice characteristics)
SEOM 97.1%	100% documentation	Episodes (n) 73.5%	Rapid onset
ESMO 63.2%	99% best evidence	Pain intensity 66.3%	High potency
NCCN 58.8%	99% specific medication	Duration 45.8%	Short duration
Instit 19.1%	99% fentanyl 1st choice	Time to peak 30.1%	Route of administration
Other 7.3%		Triggers 75.9%	Ease of use
		Relief strategies 73.5%	Minimum side effects
		Etiopathogenia 86.7%	

Table: 1589P

Program	% at risk interested in program	Believe Program is Beneficial			Believe in Routine Care Program		
		Agree	aOR of being interested (95% CI)	*P*	Agree	aOR of being interested (95% CI)	*P*
Smoking Cessation	53%	57%	2.85 (1.0-7.9)	0.04	63%	4.80 (1.7-13.9)	0.004
Household Smoking Cessation	37%	55%	2.73 (1.1-6.7)	0.03	58%	4.60 (1.8-11.9)	0.002
PA	53%	70%	4.73 (2.5-9.0)	< 0.001	71%	3.33 (1.8-6.3)	< 0.001
Alcohol Moderation	25%	55%	2.54 (1.3-5.1)	0.01	61%	2.27 (1.2-4.6)	0.02

Methods: 501 cancer pts from all subtypes were surveyed on their smoking, PA and alcohol consumption patterns along with their interest and perceptions for programs for these behaviors. Multivariable logistic regression models identified factors associated with pt interest and perceptions.

Results: At diagnosis, 115 pts smoked; 41% had second hand smoke (SHS) exposure; 238 were drinking alcohol; 313 did not meet PA guidelines. At risk individuals' (e.g, smokers for smoking cessation, exposed to SHS for household smoking cessation) survey results are shown in the table. Perceptions of how these behaviors impact quality of life, survival and fatigue was not associated with program interest ($P > 0.05$). However, pts perceiving that alcohol worsened and PA improved these outcomes were more to likely believe associated programs are beneficial (alcohol aORs = 2.1-2.2 $P < 0.03$; PA aORs = 1.9-3.2 $P < 0.02$) and should be routine care (alcohol aORs = 1.9-3.5 $P < 0.03$; PA aORs = 1.7-2.4 $P < 0.1$). Pts with more pack-yrs less likely perceived benefit in a household cessation program (aOR = 1.02 $P < 0.007$) or in a routine care program (aOR = 1.01 $P < 0.02$). Pts preferred discussing programs with doctors (35%+) or counsellors (42%+).

Conclusions: About half of pts feel that lifestyle behavior programs would be beneficial and should be part of routine care. These factors were more important than perception of the behaviors on outcomes in influencing pt interest. Initial discussions with pts should focus on discussing benefits of these programs.

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Disclosure: All authors have declared no conflicts of interest.

1590P The investigate relationship between severe neutropenia and ABCB1and ABCG2 gene polymorphisms with esophageal cancer patients receiving docetaxel, cisplatin and 5-fluorouracil chemotherapy

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Background: The combination of docetaxel, cisplatin and 5-fluorouracil (DCF) is a newly developed chemotherapy for esophageal cancer (EC) patients (pts). Severe neutropenia is one of the major adverse events that necessitate chemotherapy dose reduction. This study aimed to investigate relationship between grade 3 and 4 neutropenia and genetic polymorphisms in EC pts received DCF.

Methods: EC pts who had undergone DCF chemotherapy at National Cancer Center Hospital East from August 2011 to December 2016 were enrolled in this study. Prophylactic administration of granulocyte-colony stimulating factor was not conducted for the all EC pts during the above chemotherapy. Seven polymorphisms in the genes encoding docetaxel-metabolizing enzymes and transporters were genotyped, and then relationship between these genotypes and the grade 3 and 4 neutropenia was then investigated. Risk factors that enable to predict grade 3 and 4 neutropenia after first cycle of chemotherapy were explored using multivariate logistic regression analysis.

Results: A total of 170 pts treated with DCF were enrolled in this study period. The median age was 64 years, median body mass index was 22.0 (15.3 - 31.0), median serum hemoglobin level was 13.5 (8.7 - 17.1) g/dL, median prognostic nutritional index was 50.1 (36.7 - 68.7) and baseline absolute neutrophil count (ANC) was 4305 (1660 - 11020)/mm^3. The proportion of pts with grade 3 and 4 neutropenia was 56 (32.9%) and 34 (21.2%), respectively. Multivariate logistic regression analysis adjusted for potential risk factors revealed *ABCB1* 3435C > T ($p = 0.015$), *ABCG2* 34G > A (p=0.044), age (60<) ($p < 0.001$) and baseline ANC (< 4305) ($p = 0.001$) were independent and significant risk factors for grade 3 and 4 neutropenia.

Conclusions: We identified that genetic polymorphisms in ABCB1 3435 C > T and ABCG2 34 G > A was a significant predictor for grade 3 and 4 neutropenia of EC pts receiving DCF.

Legal entity responsible for the study: National Cancer Center Hospital East

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1591P Hepatitis B and C reactivation rates due to cytotoxic chemotherapy in patients with solid tumors

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Background: We tried to determine the incidence of the reactivation rates of chronic HBV and HCV infections in cancer patients who received different types of chemotherapy or immunosuppressive therapy. Also we tried to identify the chemotherapy regimens though to be associated with this reactivation of chronic HBV and HCV infections.

Methods: Between 2000 and 2014, 8322 cancer patients who were admitted to oncology departments were evaluated retrospectively and 3890 patients in whom hepatitis serology were available were included in this study. Their mortality rates, chemotherapy regimens, cancer types, number of positive hepatitis serology and reactivation rates were also obtained.

Results: In all 8322 cancer patients, only 3890 (47%) patients had hepatitis serology results and 355 patients had positive hepatitis serology results (HBsAg, anti-HBcAg, anti-HCV). Of them, 4.24% had anti-HBcAg positivity, 3.65%had HBsAg positivity, and 1.23% had anti-HCV positivity. Nineteen patients with HBsAg positive (13.38%), 4 patients with anti-HBcAg positive (2.42%), and 2 patients with anti-HCV positive (4.16%) had reactivation. hepatitis reactivation was seen significantly higher in lymphoma patients ($p = 0.032$). Reactivation rate of hepatitis B in those patients (HBsAg positive) was detected as 57.14%. In patients with hepatitis reactivation, the rates of usage of 5-FU, cisplatin, cyclophosphamide, doxorubicin, steroid, rituximab, and vincristine were determined as significantly higher than patients with positive hepatitis serology results but without hepatitis reactivation ($p > 0.05$ for all).

Conclusions: An association between hepatitis reactivation and the usage of 5-FU, cisplatin, cyclophosphamide, doxorubicin, steroid, rituximab, and vincristine was detected. Thus physicians should consider antiviral prophylaxis before initiating these chemotherapeutics.

Legal entity responsible for the study: Individuals: Ahmet Ozet, Deniz Tural

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1592P Meta-analysis of individual patient safety data from six randomized, placebo-controlled trials with the antiangiogenic VEGFR2-binding monoclonal antibody ramucirumab

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Background: Ramucirumab, a human IgG1 monoclonal antibody receptor antagonist of vascular endothelial growth factor receptor 2 (VEGFR-2), has been approved for treatment in gastric/gastroesophageal junction, non-small cell lung, and metastatic colorectal cancers. A total of 6 global, randomized, double-blind, placebo-controlled, phase 3 trials across multiple tumor types and a large patient population have currently been completed. To further establish the safety profiles of ramucirumab, a meta-analysis has been performed based on the data from these 6 trials and the results are presented here.

Methods: Fixed-effects or mixed-effects models were used to conduct an individual patient meta-analysis across the 6 completed phase 3 trials and derive the relative risk (RR) and associated 95% confidence intervals (CIs) for all-grade and high-grade (Grade $\geq$3) adverse events (AEs) possibly related to VEGF pathway inhibition.

Results: This meta-analysis included a total of 4996 treated patients (2748 patients in ramucirumab arms, 2248 in control arms). Proteinuria, gastrointestinal (GI) perforation, hypertension, wound-healing complications, infusion-related reactions, and low-grade (Grade 1-2) bleeding were observed at a higher percentage in the ramucirumab arms compared to control. However, our data did not demonstrate a definite increased risk with ramucirumab in high-grade bleeding (RR: 1.1, 95% CI 0.8-1.5), high-grade GI bleeding (RR: 1.1, 95% CI 0.7-1.7), venous thromboembolic events (VTE, all-grade, RR: 0.7, 95% CI 0.5-1.1; high-grade, RR: 0.7, 95% CI 0.4-1.2), or arterial thromboembolic events (ATE, all-grade, RR: 0.8, 95% CI 0.5-1.3; high-grade, RR: 0.9, 95% CI 0.5-1.7).

Conclusions: The risk of developing certain AEs with ramucirumab is consistent with other antiangiogenic agents; and, the safety profile is consistent with the ramucirumab labels. Our results showed no clear evidence for an increased risk of high-grade bleeding, high-grade GI bleeding, VTE, or ATE in this large and patient level meta-analysis.

Clinical trial identification: REGARD = NCT00917384, RAINBOW = NCT01170663, REVEL = NCT01168973, RAISE = NCT01183780, REACH = NCT01140347, ROSE = NCT00703326

Legal entity responsible for the study: Eli Lilly and Company

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1593P The preventive role of intravenous L-alanyl L-glutamine in reducing the incidence of oral mucositis in head and neck cancer patients receiving radiotherapy with or without chemotherapy

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Background: The current prospective comparative phase 2 study aimed to assess the role of intravenous L-alanyl L-Glutamine in reducing the rate of oral mucositis for squamous head and neck cancer patients receiving radiotherapy with or without concurrent chemotherapy.

Methods: From September 2014 to Septemper 2016, 100 head and neck cancer patients were treated with radiotherapy or combined chemo-radiation at the Clinical Oncology Department, Tanta University Hospitals. Patients were randomized in 1:1 ratio into Group A (n = 50 patients) treated by radiotherapy or concurrent chemo-radiotherapy and Group B (n = 50 patients) to receive same treatment in addition to intravenous Glutamine. The investigational drug was infused daily at dose of 0.3-0.4 g/kg diluted in NS and administered at rate of 0.1g/Kg/hr. All patients received total dose of 65-70 Gy using Linac 6MV photon beam supplemented with electron beam when needed. For concurrent chemotherapy, Cisplatin (40mg/m2) was administered weekly.

Results: Mucositis was assessed by WHO grading system. A significantly higher incidence of mucositis was reported in 45% of Group A patients compared with patients in group B who received glutamine 10% $P < 0.001$). Group B patients had significantly longer period free from mucositis in comparison to group A with median time (12 weeks vs 8 weeks) $P < 0.001$. A significant lower rate of radiotherapy interruption was reported in group B compared to group A (50% vs 15%) $P < 0.001$. More Patients needed hospitalization in group A (20%) vs (5%) in group B $P = 0.059$. No adverse effects were observed in relation to glutamine.

Conclusions: Intravenous L-alanyl L-Glutamine may be an effective measure to lower incidence or prevention of oral mucositis in head and neck cancer patients treated by radiotherapy or combined chemo-radiation.

Legal entity responsible for the study: Tanta University Hospital

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1594P Biosimilar epoetin alfa (HX575) for the treatment of chemotherapy-induced anaemia: Development, approval and 10 years' clinical experience

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Background: Patent expirations for biological products have prompted the development of biosimilars, which have comparable quality, safety and efficacy to a licensed biological medicine (the 'reference' medicine). HX575 (Binocrit®, epoetin alfa biosimilar) was approved in Europe in 2007 for the treatment of chemotherapy-induced anaemia (CIA).

Methods: The development and approval of HX575 included extensive analytical characterisation and comparison with the reference epoetin alfa, followed by a clinical development programme; this included phase I pharmacokinetic/pharmacodynamic studies to show bioequivalence to the reference medicine, and a confirmatory phase III study to confirm therapeutic effectiveness in CIA. Since approval, HX575 has been extensively used in real-world clinical practice.

Results: An array of analytical methods confirmed the similarity of HX575 and the reference epoetin alfa in terms of primary protein structure, higher-order protein structure, isoform pattern, post-translational modifications, receptor binding and biological activity. Phase I studies showed that HX575 and the reference medicine were bioequivalent following intravenous and subcutaneous administration. In a confirmatory phase III study (n = 114), HX575 was effective in treating CIA in cancer patients, and had a safety profile consistent with the therapeutic class and as expected for the therapeutic area. Post-approval data are also available for a range of cancer types; positive results have been reported from a multi-centre retrospective clinical study, single-centre experiences from several countries, and a large-scale prospective observational study. No additional/unexpected safety issues have emerged after 10 years of pharmacovigilance. A pilot study has suggested that HX575 may also be effective for the treatment of anaemia in low-/intermediate-1 risk myelodysplastic syndromes.

Conclusions: As of Feb 2017, HX575 has generated >252,000 patient years' experience in CIA worldwide. Accumulated data and experience over a decade are reassuring that

HX575 is effective and well tolerated for the treatment of CIA in patients with different cancer types.

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1595P Experience with the implant of vascular access devices by medical oncologist in a non-surgical scenery

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Background: Totally implantable central venous catheters are widely used in the management of patients (pts) with malignant diseases in order to facilitate drug delivery for the new therapeutic protocols. These are based on continuous administration and higher doses of chemotherapeutic agents with relative phlebitis problems and supportive treatment. Staff of our department, specially trained on the routinely implant of central venous accesses were in charge of the procedure. The technique was carried out under local anesthesia in a special suite of day hospital, under strict aseptic measures without fluoroscopic control.

Methods: From Sep 94 to January 2017, 1665 devices (port-a-cath systems [PS]) were implanted in 1627 pts, with a median age of 50.5 yr (range 14-81), and median K.I. 70% (50-100), female 982/male 683. Venous access: right interior jugular 983, left subclavian 316, right subclavian 333, left interior jugular 33. A thorax X-ray was performed after each procedure and in 216 pts prophylactic antibiotics were given.

Results: The venous access remained implanted a median of 438 days (1- +2210). Complications occurred in 266 placements (16%): Infections 116 (7%); deep venous thrombosis 66 (4%) obstruction 10 (0.6%); malpositioned 16 (2%); fractures/migration 28 (1.7%); pneumothorax 6 (0.32%); local skin necrosis 7 (0.6%). Five hundred and twenty devices were removed, three hundred and forty-seven (66%) after completing planned therapy and 173 (34%) due to complications [Infections (92), migration (22), malposition (12), venous thrombosis (26), obstruction (11) and skin necrosis (10)]. Cost-effectiveness of venous catheters in a non-surgical scenery compared to devices implanted by interventional vascular radiologists in operating room turned out to be 1000 euro cheaper for each device.

Conclusions: Our experience suggests that implant of vascular access devices by medical oncologist in a non-surgical scenery has similar or even less complications and is more cost effective with regard to radiology suite and operating room placement procedures.

Legal entity responsible for the study: Emilio Esteban, Oncología Médica, Hospital Universitario Central de Asturias.

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1596P Management of chemotherapy-related side effects- do patients know where to get help?

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Background: Timely access to oncology healthcare providers for advice about chemotherapy-related symptom management is a provincial priority in Ontario, Canada. The aim is for all chemotherapy patients to have access to an oncology care provider for urgent advice thereby reducing unscheduled visits such as emergency room (ER) attendance and hospitalizations which are common during chemotherapy. Here, we explore patients' knowledge about how to access urgent advice for side effects.

Methods: Between September and November 2016, 4 hospitals providing systemic therapy in Toronto, Canada (one academic & three community centers) performed a program evaluation for quality improvement purposes. A paper survey was developed. Patients with breast, lung, gastrointestinal, hematological cancers and sarcoma $\leq$4 weeks after their first chemotherapy cycle were questioned in chemotherapy day units. The survey explored patients' knowledge about where to get help for chemotherapy related side effects at different time points (weekdays 9am-5pm, weekdays 5pm-9am, weekends). Descriptive statistics and Chi square were used to describe results.

Results: A total of 140 surveys were administered to 32 lung, 38 breast, 39 GI, 22 hematology and 9 sarcoma patients. Overall, 81% of patients stated they knew where to go to get help for side effects; 56% of patients were told where to get help by a staff member, usually a nurse (44%) or oncologist (23%), while 19% reported they were not told where to get help by anyone. Across all time points the majority of patients stated they would present to ER for side effect management (41, 76 & 81% respectively). The only exception was the academic hospital where 69% of patients reported calling the clinic/nursing telephone line on weekdays 9am-5pm (comparison between academic and community centers $p < 0.001$). Qualitative analysis of comments revealed that patients want more resources and education in easily accessible formats and prefer to speak to a person rather than leaving voice messages.

Conclusions: Significant gaps in patient care and education are highlighted by these results. Site specific quality improvement projects are currently underway to address these findings prior to re-administering the survey.

Legal entity responsible for the study: Regional Systemic therapy program

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1597P The effects of nurses' empathy skills on attitudes towards patients with cancer

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Background: Empathy is sine qua non-ability of nurses and the positive effects of empathy on clinical management have been documented. In addition, its positive effects have also been reported in oncology practice. The purpose of this study is to evaluate the predictors of empathy skills and attitude towards cancer patients and association between nurses' empathy skills on attitudes towards patients with cancer.

Methods: A structured questionnaire was used to evaluate the nurses' empathy skills and their attitudes towards to patients with cancer. Jefferson Scale of Empathy(JSE) and Attitudes Towards Cancer Scale (ATCS) were used. The predictors of JSE/ATCS scores and correlation between JSE and ATCS were analyzed.

Results: 305 nurses participated in the study (84.2% of all nurses). The median age was 33 (20-52) and most of the nurses were female (82.6%). Most of the participants were married (188,61.6%) and 40.3% of nurses had an job experience more than 10 years. Female sex, being married, having job experience more than 10 years or caring more cancer patients were associated with higher JSE scores. Nurses caring more cancer patients weekly, experience with cancer patients, participation in educational activities about cancer care or presence of relative with a diagnosis of cancer were found to have more positive attitudes towards cancer patients. Spearman correlation analysis showed a positive, weak correlation between JSE and ATCS ($r = 0.017$, $p = 0.38$)

Conclusions: Empathy skills are important while caring patients, especially in oncology practice. Although a direct correlation between empathy skills and attitudes towards cancer patients couldn't be demonstrated, health care workers caring cancer patients should be both evaluated for empathy skills and educated.

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Disclosure: All authors have declared no conflicts of interest.

1598P Can postponement of death be used in shared decision making in patients treated with adjuvant chemotherapy?

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Background: Standard adjuvant treatment to patients with stage III colon cancer is six months of adjuvant combination chemotherapy with a 5-fluorouracil derivate (5-FU) and oxaliplatin. In some cases, 5-FU monotherapy may be an option. The aim is to develop a different way of explaining the benefit of different treatment options by using the concept of "postponement of death".

Methods: We identified pivotal phase III publications about adjuvant treatment for stage III colon cancer. Data regarding overall survival was extracted for observation versus 5-FU monotherapy and combination chemotherapy versus 5-FU. Data about the impact of N1 and N2 category was extracted if available. Data was used for restricted mean survival analysis. Postponement of death was defined as the mean difference in survival time between the two randomized treatment arms. Survival curves was plotted

into the tool WebPlotDigitizer and the area under the curve (AUC) was calculated for each treatment.

Results: AUC for patients receiving 5-FU was 69.1 months and for combination chemotherapy 71.9 months. The mean survival difference at 10 years was 2.8 months. For the subgroup of patients with N1 category, the postponement of death was 0.5 months if treated with combination chemotherapy instead of 5-FU. For patients with N2 category the difference was 11.6 months when treated with combination chemotherapy compared to monotherapy. In the trial comparing 5-FU with observation, the AUC was 73.7 months and 63.3 months, respectively, at 8.5 years. The overall postponement of death between 5-FU and observation was 10.4 months not adjusted for N status.

Conclusions: Postponement of death can be calculated using restricted mean survival analysis and published survival curves. Patients with colon cancer stage III can be advised that up to 6 months of 5-FU will postpone death on average 10 months compared to observation alone. Adding oxaliplatin will postpone death an additional 3 months with no adjustment for N status. Oxaliplatin has minor effect in N1 category (2 weeks) and major effect in N2 category (12 months). Future studies should investigate how the concept of postponement of death can be implemented in daily clinical practice.

Legal entity responsible for the study: Natacha Dencker Trabjerg

Funding: Department of Oncology Vejle Hospital, Center of Clinical Excellence, Danish Colorectal Cancer Center South Denmark

Disclosure: All authors have declared no conflicts of interest.

1599P Cancer patient attitudes and preferences towards smoking status assessment

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Background: Continued smoking after a cancer diagnosis is associated with poorer outcomes. As smoking cessation is an important part of cancer care, understanding cancer patient (pt) attitudes towards smoking status assessment will help with integrating smoking cessation programs into cancer care.

Methods: Cancer pts from all subtypes were surveyed on their smoking history, assessment rates and attitudes/preferences towards smoking status assessment. Multivariate logistic regression models helped assess for factors associated with screening preferences.

Results: Among 501 pts, 115 smoked at diagnosis and 60% quit after; 53% had a tobacco related (lung/head and neck) cancer (TRC); 64% were treated curatively; 40% reported that their smoking status was assessed only on their first clinic visit, while 32% were assessed at a few visits and 12% all visits. Most felt that smoking status should be assessed at the first visit (95%), while half (58%) felt it should be assessed every visit. Most felt comfortable with being assessed (96%), felt it was important for clinicians to be aware of smoking status (98%) and that smoking cessation discussions should occur at the first visit (87%). Most preferred being assessed by their oncologist (88%); less than half preferred being asked by another healthcare provider (44%), on paper (29%) or electronic surveys (32%). When compared to ex/never smokers, current smokers were assessed more often at every/most visits (36% vs 20% $P = 0.001$); fewer felt assessment should occur at the first visit (89% vs 97% $P = 0.008$) and were less comfortable with being assessed (88% vs 98% $P < 0.001$). Among current smokers, lung cancer pts were more agreeable (54%) to being assessed every visit compared to head and neck (aOR = 2.45 95% CI [0.9-6.5] $P = 0.06$) and non TRCs (aOR = 2.63 [1.0-6.8] $P = 0.05$). Among all, pts who are older (aOR = 1.03 [1.0-1.1]), curative (aOR = 1.92 [1.1-3.2]) and smoked less (aOR = 0.98 per pkyr [0.97-0.99]) were more agreeable to assessment at each visit.

Conclusions: Most cancer pts felt that assessment of smoking status was important, were comfortable with being assessed and preferred being assessed directly by their oncologist. Routine screening of those currently smoking is recommended to help with cessation.

Legal entity responsible for the study: Princess Margaret Cancer Centre

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1600P Optimizing Physician Surveys in Pharmacovigilance Using ecancer Online Community

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Background: Physician knowledge surveys have increasingly been requested of drug manufacturers in the post-authorization setting as part of risk minimization plans. Surveys in pharmacovigilance require considerable time and resource, and result in low response rates and questionable representativeness. After EMA consultation, an educational programme was initiated with *e*cancer to evaluate the potential of online communities in measuring knowledge of drug safety risks. Here, we describe the baseline survey used to measure basic knowledge of osteonecrosis of the jaw (ONJ) risks among prescribers of bone targeting agents (BTAs).

Methods: Clinical experts developed 8 multiple choice questions on BTAs and ONJ risk as described in the summary of product characteristics. BTAs included denosumab, zoledronate, or pamidronate. Invitations were sent out to ecancer and ECCO members. Eligible were physicians who treated ≥5 new/continuing adult patients with bone metastases from solid tumours in the last 3 months (mos), currently practicing as an oncology specialist in the European Union, Switzerland or Norway, and prescribed a BTA in the last 12 mos. Responses for eligible and ineligible were compared.

Results: Among visits to the online survey, 87% completed the questions: 336 eligible/ineligible respondents from 52 countries, 292 from 26 European countries. Ineligibility was driven by the criterion of treating ≥5 patients in last 3 mos. Eligible respondents (n = 182) had higher level of correct responses than those who did not meet eligibility: mean 81% vs. 73% ($p < 0.01$) (Table). Question 3 yielded lowest correct responses on the topic of ONJ incidence as reported in BTA clinical trials.

Table: 1600P

Question Number	Eligible (n = 182), Correct Responses	Ineligible (n = 110), Correct Responses
1	83%	80%
2	93%	91%
3	52%	43%
4	85%	61%
5	91%	84%
6	80%	92%
7	81%	77%
8	85%	73%

Conclusions: Online professional communities offer a pragmatic and efficient approach for recruitment of physicians for knowledge assessments. Basic knowledge of ONJ risks was high overall in this ecancer proof of concept. The strategy can achieve responses representative of today's physicians who seek information online. These findings may be compared with knowledge among physicians who may not seek information online.

Legal entity responsible for the study: ecancer

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1601P Ideal cardiovascular health (ICVH) in patients with a recent diagnosis of colorectal cancer (CRC)

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Background: Cardiovascular events are an important cause of mortality in patients cured of colorectal cancer and are also potential complications of new therapies for metastatic CRC. The American Heart Association's "Simple 7" offers a practical public health conceptualization of cardiovascular health. They include healthy behaviours: non-smoking, active physical activity (MVPA > 150 min/w), healthy diet and low body mass index (BMI); and health factors: no hypertension, no diabetes, no hypercholesterolemia. Whereas factors are non-modifiable, behaviours can be changed. Studies have shown that prevalence of ideal cardiovascular health in the US is only 0.1%.

Methods: Patients with a recent diagnosis of CRC who accepted to participate were prospectively evaluated. BMI, blood pressure, glucose and cholesterol were measured at the hospital. Physical activity was objectively evaluated with accelerometers. Adherence to a healthy diet was evaluated through the PREDIMED (adherence to Mediterranean diet) questionnaire. Information about smoking and past cardiovascular disease or risk factors was obtained from the clinical record.

Results: 91 patients were recruited between March 15 and March 17. 36% were metastatic. Age 65 (25-81), 69% male 31% female, BMI 26.2 ±3.6, Waist 95,6 ±12 cm, mean MVPA 350±248 min/wk, mean sedentarism 3394±1123. 9% had a history of CV disease (ischemic, cerebrovascular, heart failure). 34% were classified as high CV risk. Only one patient showed an ICVH.

Table: 1601P

		Healthy behaviours				Health Factors		
ICVH	No CV history	Nonsmoking	BMI <25	Healthy Diet	MVPA	No HTA	No DM	No DL
1.1%	91%	90.5%	36%	67%	96%	51%	84.3%	66%

Conclusions: The prevalence of ICVH in a population of Spanish CRC patients was 1%. This population was overall compliant with PA recommendations, adhered to a healthy diet and less than 10% smoke in the last year. Hypertension was the most prevalent risk factor. Overweight was the most prevalent unhealthy behaviour. Interventions should be aimed at reducing BMI. Interventions exploring programs with vigorous physical activity and diet modifications in CRC survivors are warranted.

Legal entity responsible for the study: Ana Ruiz-Casado

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1602P Additive effect of vinca alkaloids as the risk factor for hearing impairments in the childhood cancer survivors

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Background: The survival rate of childhood cancer is approaching to over 80%, and survivorship is gathering more attention. The survivors receive chemotherapy, radiotherapy and surgery in their early life stages, and the risk of ototoxicity is increased. We evaluated the degree of risk of the clinical factors causing the ototoxicy, in childhood cancer survivors.

Methods: We established survivorship program for late effects in Yonsei Cancer Center, Seoul, Korea. In all 531 enrolled survivors in the clinic, 105 patients were invited to evaluate otoxocitity in their bi-annual visits and the clinical risk factors were reviewed retrospectively.

Results: The median age at diagnosis was 6.0 (0∼26). Most common diagnosis was leukemia/lymphoma (N = 30, 30%), and brain tumor was the next (N = 29, 29%). Platinum agents were used in 64%, alkylating agents was in 83% and vinca alkaloid was in 78%. Severe hearing impairments defined as over than 60 dB loss were observed in 37% of left ears and 39% of right ears. The proportion of the survivors who had 20 dB loss in any side of ears was 28%. The 69% of abdomen tumor survivors and 56% of brain tumors had any of hearing impairments, but only 28% of leukemia/lymphoma survivors showed hearing loss ($P < 0.001$). The class of platinum agents use, vinca alkoids were adverse factors, however, the class of antimetabolites use or antibiotics use were all protective factors for hearing impairments ($P < 0.001$, <0.001, 0.006, <0.001, respectively). Both use of platinum and vinca alkaloids showed significantly higher risk of hearing impairments compared with use of none or one class of two classes of agents ($P < 0.001$ for right ear and $P < 0.001$ for left ear). Young age at diagnosis (<7.5 years old) showed higher risk of hearing loss in abdomen tumor and brain tumor group ($P = 0.006$ for right, $P = 0.051$ for left). Total 5000 cGy or more of head and neck region radiation showed increased risk ($P = 0.001$ for right, $P = 0.007$ for left). In multivariate analysis, both use of platinum and vinca alkaloids was independent risk factor (O.R.=8.1, $P = 0.004$ for right; O.R.= 8.7, $P = 0.004$ for left).

Conclusions: Hearing impairments were common late effects in childhood cancer survivors, and vinca alkaloids had additive adverse effects on the platinum use for the hearing loss.

Legal entity responsible for the study: Jung Woo Han

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1603P Development and validation of chewing swallowing inventory (CSI) in head and neck cancer patients

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Background: Chewing and swallowing dysfunction are the common problems in head and neck cancer patients. They may interfere patients' eating and lead to malnutrition. An easily used tool to assess the problems is needed. The purposes of the study were to (1) develop the Chewing Swallowing Inventory (CSI) and (2) examine the psychometric properties of CSI.

Methods: This is an instrument development and testing study. We recruited adult patients with head and neck cancers in the head and neck cancer outpatient clinics in the medical center in northern Taiwan. The items of CSI was developed based our previous research results, clinical observation, literature review and preliminarily validated by experts panel. Psychometric testing includes content validity, internal consistency reliability, construct validity by examining of its factor structures (exploratory factor analysis), theoretical supported correlation and discriminated constructs by groups.

Results: The CIS was a 21-item 0 to 4 Likert's typed scale with 0 representing "no problem/difficulty at all" and 4 representing "having extremely severe difficulty". We recruited 175 patients. The results showed that (1) CSI has good internal consistency reliability with Cronbach's α value as 0.93. (2) The factor analysis suggest that CSI contains four clear factors which are chewing, swallowing, tongue moving/stirring and taste and saliva changes which explained 70.32% of variances. (3) CSI has good construct supported correlation with nutrition. (4) CSI had good discriminate validity to differentiate patients with different diagnosis, surgical modalities, treatments, and disease stages.

Conclusions: CSI is a simple, easily used, reliable and validated tool to assess patients' eating difficulties. It will better support health care professionals to detect HNC patients' eating related chewing and swallowing problems and provide personalized intervention to prevent malnutrition.

Legal entity responsible for the study: National Taiwan University Hospital

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1604P The Relationship between Oral Supportive Care and Oral Complications in Cancer Patients Receiving Chemotherapy: A Retrospective Study

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Background: Oral supportive care for cancer patients received medical insurance coverage in 2012 in Japan. Management includes not only prevention of wound infection and perioperative pneumonia but also treatment of oral complications during chemotherapy and radiotherapy in cancer patients. We conducted a retrospective study to analyze the efficacy of oral supportive care for cancer patients receiving chemotherapy.

Methods: We retrospectively analyzed consecutive 1,142 cases received anticancer chemotherapy in our hospital from April 2013 to March 2017.

Results: Patients were 633 males and 509 females aged 23-92 years (median 66). Primary sites were lung in 246, esophagus in 193, breast in 137, head and neck in 112, and others in 454. Treatment was chemotherapy in 752, and concurrent chemoradiotherapy in 390. Before beginning chemotherapy, all patients received a dental check and acquired tooth brushing techniques. We compared the oral hygiene status in 752 patients before the beginning of therapy and at the 1-month check. Rates of improved, stable and regression status were 56.9%, 23.5%, and 19.6%. Regression appeared due to worsening of general condition, and also to oral mucositis among head and neck cancer patients. Oral supportive care was continued to maintain good oral hygiene, detect oral

complications early and manage them with dental treatment, dental extraction, mechanical cleaning, medicine, mouthwash and topical ointment and analgesics. Oral complications of ≥ Grade 3 (NCI-CTC AE ver. 3.0) were antiresorptive agents-related osteonecrosis of the jaw, teeth infections, and oral mucositis occurred during treatment. There was a significant difference in the incidence of oral complications between more and less than 3 months from the latest dental visit at the start of chemotherapy ($p < 0.02$).

Conclusions: Oral supportive care for cancer patients receiving chemotherapy should begin before the start of treatment and continue until the successful completion of treatment, especially for the deteriorated patients, head and neck cancer patients, and patients who did not receive dental checkups and cleaning for more than 3 months.

Legal entity responsible for the study: Kobe Minimally Invasive Cancer Center

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1605P Safety and effectiveness of sensor-controlled scalp cooling in women receiving chemotherapy for primary breast cancer

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Background: Sensor-controlled scalp cooling (SCSC) to prevent chemotherapy-induced alopecia (CIA) in patients (pts) with primary breast cancer (PBC) is approved by the FDA. However, SCSC isl infrequently used in many countries due to concerns regarding both safety and feasibility. This retrospective analysis sought to obtain more detailed information about the effectiveness and safety of SCSC using the Paxman system (Paxman, Huddersfield, UK) in PBC pts exposed to neoadjuvant (NACT) or adjuvant Ctx (ACT) in the clinical routine.

Methods: 79 pts were identified from our database: NACT, 41 (51.9%); ACT, 38 (48.1%); dose-dense (dd) Ctx, 56 (70.9%); non-dd Ctx 23 (29.1%); premenopausal, 44 (55.7%); postmenopausal, 35 (44.3%). The following Ctx regimens were used: anthracycline-based (A), 1 (1.3%); taxane-based (T), 21 (26.6%); AT-based, 55 (69.6%); non AT-based, 2 (2.5%). Pts were subjected to SCSC during each Ctx cycle. CIA was quantified using the Dean score (DS) determined 3 wks after the last Ctx cycle. Data were analyzed regarding the SCSC completion rate, quality of hair preservation (success: DS 0-2, failure: DS 3-4), reasons of SCSC discontinuation, and toxicity. Moreover, the following parameters were investigated in regard to the success of SCSC: menopausal status, NACT vs ACT, dd Ctx vs non-dd Ctx, AT-based Ctx vs A-/T- or non-AT-based Ctx.

Results: 55 pts (69.6%) completed SCSC with 36 (45.6%) showing complete (DS 0), and 19 (22.8%) showing partial success (DS 1-2). 24 pts (30.4%) discontinued SCSC with CIA seen in 18 pts (22.8%). Headache and local discomfort ("feeling cold") were reported in 4 pts (5.1%) each. Side effects were all not severe and resolved quickly after cessation of SCSC. SCSC was equally effective in all analyzed subgroups. The relative risk (RR) to experience CIA was 1.11 (CI: 0.82-1.54) for post- vs premenopausal pts; 1.11 (CI: 0.83-1.53) for ACT vs NACT; 1.31 (CI: 0.96-1.72) for AT vs other Ctx protocols, and 0.99 (CI 0.72-1.43) for dd Ctx vs non-dd Ctx.

Conclusions: In our study, SCSC was safe and effective to prevent CIA in PBC pts. The success rate in our study is in good agreement to previous randomized trials of SCSC in PBC arguing in favor that SCSC is a valuable supportive treatment in the clinical routine.

Legal entity responsible for the study: Christian M. Kurbacher

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1606P Pharmacokinetics and safety of FOLFOX therapy in patients undergoing hemodialysis

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Background: Due to a lack of information, there is no guideline regarding the dosage and timing of chemotherapy in cancer patients undergoing hemodialysis (HD). Therefore, we studied the pharmacokinetics of 5-fluorouracil (5-FU) and oxaliplatin (L-OHP) in cancer patients undergoing HD.

Methods: HD patients (HD group) and patients with normal renal function (control group) who had received either modified FOLFOX6 therapy or modified FOLFOX7 therapy were prospectively enrolled. The blood concentrations of 5-FU and 5-FU metabolites, including α-fluoro-β-alanine (FBAL), fluoroacetic acid, and ammonia were measured using inductively coupled plasma-mass spectrometry. The blood concentrations of total and ultrafilterable platinum were measured in the HD group. To estimate the amount of L-OHP removal by dialysis, we also measured the platinum concentration in dialysate.

Results: There were six patients in the HD group and eight patients in the control group. In the HD group, L-OHP was administered just before the HD session in four patients, and on a non-dialysis day in two patients. The amount of L-OHP removal by dialysis was 10% or less of the administered dose, and did not depend on the timing of L-OHP administration. Regarding the 5-FU metabolites, the blood concentration of FBAL was significantly higher in the HD group than in the control group ($p < 0.01$). We observed hyperammonemia in two patients in the HD group, which was accompanied by elevated blood levels of FBAL and fluoroacetic acid, and was therefore considered to be related to 5-FU administration. Conscious level deterioration was observed in one patient with hyperammonemia.

Conclusions: The amount of L-OHP removal by dialysis was up to 10% regardless of the timing of L-OHP administration. Hyperammonemia should be monitored during FOLFOX therapy among HD patients.

Legal entity responsible for the study: Onco-nephrology Consortium

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1607TiP J-FORCE study: A randomized, double-blind, placebo-controlled phase III study evaluating olanzapine (5 mg) combined with standard antiemetic therapy for the prevention of chemotherapy-induced nausea and vomiting in patients receiving cisplatin-based, highly emetogenic chemotherapy

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Background: In the Alliance A221301 study, olanzapine (OLZ; 10 mg) significantly improved the prevention of nausea in patients who were receiving highly emetogenic chemotherapy (HEC). However, growing concerns exist concerning somnolence and sedation. We previously reported on the efficacy and safety of two doses (5 mg and 10 mg) of OLZ in combination with aprepitant (APR), palonosetron (PALO), and dexamethasone (DEX) in patients receiving HEC. OLZ (5 mg) seemed to lead to lower somnolence than OLZ (10 mg) and was equally effective in preventing nausea. The aim of this phase III study is to evaluate the efficacy and safety of 5 mg OLZ doses as compared with placebo, in combination with APR, PALO, and DEX, for the control of nausea in patients receiving HEC.

Trial design: Eligibility criteria for patients include those who are aged 20–75 years, have an Eastern Cooperative Oncology Group (ECOG) performance status between 0–2, and have malignant disease who will be scheduled to receive HEC with cisplatin at a dose ≥ 50 mg/m^2. Having diabetes mellitus or being treated with antipsychotic agents within 48 hours before enrollment make patients ineligible for the study. Patients are randomly assigned to receive either a 5 mg OLZ dose or placebo orally after supper on days 1–4, in combination with APR (125 mg p.o. on day 1, 80 mg p.o. on days 2–3), PALO (0.75 mg i.v. on day 1) and DEX (9.9 mg i.v. on day 1 and 6.6 mg i.v. on days 2–4). The primary endpoint is a complete response (CR), defined as no emetic episodes and without the use of rescue medications in the delayed phase (24 to 120 hours). Secondary endpoints include a CR during acute (0 to 24 hours) and overall phases (0 to 120 hours), complete and total control rates, and the level of nausea, appetite and somnolence. A total of 690 patients are required to achieve 80% power for a one-sided significance level of 0.025. We expect the CR rate of the placebo and olanzapine arms to be 65% and 75%, respectively.

Clinical trial identification: UMIN000024676

Legal entity responsible for the study: Japan Supportive, Palliative and Psycho Social Oncology Group

Funding: Japan Agency for Medical Research and Development

Disclosure: All authors have declared no conflicts of interest.

1608TiP Heath related quality of life (HRQOL) assessment for patients with advanced renal cell carcinoma (mRCC) treated with tyrosine kinase inhibitor (TKI) using electronic patient reported outcome (PRO) in daily clinical practice

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Background: In mRCC, two therapies are mainly used in first line setting: pazopanib and sunitinib. These two TKI are equally effective in terms of survival however they are responsible for frequent adverse events. Physician mainly use RECIST progression-free survival (PFS) and NCI CTCAE safety as a guide to evaluate treatment efficiency and tolerance. In contrast HRQOL assessment is often restricted to clinical trial. It could be of particular interest to evaluate HRQOL in daily clinical practice in order to adequately choose and manage therapy. Currently the development of Information and Communication Technology may allow HRQOL monitoring in routine practice. The objective of the QUANARIE Study is to evaluate the feasibility of HRQOL assessment in daily clinical practice for patients with mRCC treated with TKI using electronic PRO.

Trial design: QUANARIE study (NCT03062410) is an interventional, prospective, multicenter trial involving 9 french oncological centers. Patients diagnosed with mRCC initiating TKI anti-VEGF treatment (Sunitinib or Pazopanib) will be invited to complete the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 cancer specific questionnaire and the EQ-5D before each visit with the physician. Questionnaires completion will be done by patients on tablets and/or computer terminals via the CHES software (Computer-based Health Evaluation System) at hospital before consultation or at home via secured portal. Physician will immediately have access to a visual summary of HRQOL evaluation. Primary objective is to assess the feasibility of routine assessment of HRQOL evaluated by the rate of filled questionnaires at 12-months. Key secondary objectives are: exhaustiveness, acceptability and effectiveness. Physician's satisfaction with electronic HRQOL evaluation will be assessed. We hypothesized that 80% of filled questionnaires at 12-months would be meaningful. A sample size of 56 patients would be needed. Enrollment is expected to last for 6 mo. Study started in April 2017. Update will be display on poster during ESMO congress.

Clinical trial identification: NCT03062410

Legal entity responsible for the study: University Hospital Jean Minjoz

Funding: Novartis

Disclosure: All authors have declared no conflicts of interest.

1609TiP Impact of a cancer care coordination program based on health information technologies for patients treated by oral anticancer therapy: The CAPRI randomized trial

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Background: The emergence of oral delivery in cancer therapeutics results in an increased need for better coordination between all treatment stakeholders, mainly to ensure adequate treatment delivery to the patient. There is a significant interest in cancer care coordination programs, especially those combining Nurse Navigators (NN) and the use of new technologies. However, the potential impact of these combined strategies is limited by a lack of rigorous evidence.

Trial design: A monocentric randomized trial (1,000 patients, 1:1) is designed to assess the impact of a cancer care coordination program namely CAPRI. This program is based on two NN and a web application. NN ensure remote patient monitoring, via phone calls and email. They also provide a link between hospital professionals, patients and primary care professionals (GP, private nurse, pharmacist, etc.) by giving them access to the web application with the patient's authorization. Patients can enter data related to their health. Alerts are sent to the NN in case of abnormal data. NN evaluate the alert level on the basis of algorithms and determine the necessary action. The study will evaluate CAPRI's efficacy in comparison with regular care during a 6-month period for adult patients with metastatic cancer. Hypothesis is that with a closer monitoring of the patient, the management of toxicities is more efficient and results in fewer dose adjustments of oral cancer therapeutics and avoids unnecessary hospital visits. The primary research aim is to assess the impact of the CAPRI program on treatment delivery for cancer patients who started oral cancer therapy, as measured by Relative Dose Intensity. The trial involves several secondary outcomes: patient adherence, tumor response, survival, toxicities, patient quality of life and patient experience. An economic evaluation adopting a societal perspective will be conducted, in order to estimate the use of healthcare resources. A parallel process evaluation will be conducted to describe the implementation of the CAPRI program. Of the 1,000 patients to be recruited, 109 patients are currently enrolled since November 2016.

Clinical trial identification: 2016-A00254-47

Legal entity responsible for the study: Gustave Roussy

Funding: National Research French Agency, Philanthropia Lombard Odier Foundation, Astrazeneca, Novartis

Disclosure: All authors have declared no conflicts of interest.

1610TiP Oncological Home-Hospitalization: Prospective randomized trial to evaluate its implications for patient and society

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Background: Home-based cancer treatment offers an integrated and patient-centered approach to deal with the challenges oncological day (care) units are facing. Current cancer therapies require frequent hospital visits that are known to be stressful for the patient and generate a high workload for hospital staff. Furthermore, these hospital visits are associated with significant costs for patients and the society, this against the background of increasing attention towards more cost-effective healthcare. Consequently, the general hospital Groeninge (Belgium) has initiated a research project to assess both, the clinical and economic impact of oncological home hospitalization. The project is supported by "Kom op tegen Kanker", a non-profit organization.

Trial design: Ambulatory treated adult cancer patients (EGOG ≤ 2 and living within a 30-minute drive of hospital) are visited at home by a clinical nurse specialist to conduct the necessary measures prior to therapy administration; that is nursing review, toxicity scoring, vital signs monitoring, blood collection, and IV line access provision. These assessments are performed one day prior to the actual therapy administration at the hospital, enabling the oncologist to prescribe and pharmacy to prepare cancer therapy before arrival of the patient. In addition, some safe experienced subcutaneous cancer therapies (i.e. bortezomib, azacitidine and trastuzumab) are administered directly at the patient's home. This new care model will be evaluated in terms of patient's quality of life, safety and cost-efficiency by performing a single-center randomized clinical trial allocating leastways 100 subjects to either home-hospitalization or standard ambulant hospital care. Currently, a non-randomized pilot study is launched in which the sensitivity of several validated patient reported outcome measuring tools is examined in both treatment settings ($n = 50$). Those instruments that show sufficient sensitivity will be included in the randomized trial. A second objective of the pilot study is to gather an extensive costs-inventory that will be used to set up an appropriate and reliable cost-analysis of home-based cancer treatment.

Legal entity responsible for the study: Koen Van Eygen

Funding: Kom Op Tegen Kanker

Disclosure: All authors have declared no conflicts of interest.

1611TiP A novel multimodal treatment strategy for cancer cachexia; rationale and motivation for the MENAC (Multimodal – Exercise, Nutrition and Anti-inflammatory medication for Cachexia) trial

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Background: Cancer cachexia is a multifactorial syndrome characterized by an ongoing loss of skeletal muscle mass that cannot be fully reversed by conventional nutritional support alone. Cachexia has a high prevalence in cancer and a major impact on patient physical function, morbidity and mortality. Despite the consequences of cachexia, there is no licensed treatment and no standard of care. It has been argued that the multifactorial genesis of cachexia lends itself well to therapeutic targeting through a multimodal treatment. Following a successful phase II trial, a phase III trial is underway.

Trial design: MENAC is a multicentre, open, randomized phase III study comparing multimodal intervention and standard cancer care versus standard cancer care alone. Patients treated for incurable lung and pancreatic cancer will be allocated randomly to receive the multimodal intervention, either immediately, or after endpoint at six weeks. The intervention is based on evidence to date and consists of Non-steroidal Anti-inflammatory Drugs (NSAID) and an EPA containing oral nutrition supplement to reduce inflammation, a physical exercise progamme consisting of both resistance and aerobic exercises to increase anabolism, as well as dietary counselling aiming to promote energy and protein balance. The overall aim is to reduce weight loss, improve food intake and maintain physical function by establish basic supportive care for cachexia. From a patient perspective, a short-term effect will be to improve physical and psychological function and reduce symptom burden. Change in body weight is primary endpoint. Secondary endpoints are change in muscle mass (CT technique) and physical activity (ActivPAL activity meter). There are several exploratory endpoints. The trial is ongoing and patients are recruited from several sites in Europa and Canada, we aim for 240 patients. If positive, the results will be practice changing for supportive treatment of patients with cancer.

Clinical trial identification: NCT02330926

Legal entity responsible for the study: NTNU through PRC is coordinating the running of the trial.

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Disclosure: All authors have declared no conflicts of interest.

1612TiP Multicenter prospective cohort study to evaluate of eye disorder induced by chemotherapy including S-1 (EyeDropS study/ HGCSG1604)

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Background: We previously reported that S-1 chemotherapy for gastrointestinal cancer (GI cancer) induced the high incidence of eye disorders (EDs), regardless of primary cancer site, treatment regimen and administration schedule (Yagisawa M, et al. 2017 Gastrointestinal Cancers Symposium). However, because this report showed a retrospective data from single institutional small cohort by reviewing medical records, we might have underestimated the incidence of EDs. So, we have conducted this prospective cohort study to confirm the incidence of EDs induced by S-1 more precisely.

Trial design: This is a multicenter prospective cohort study to evaluate the incidence of EDs and ophthalmologic changes in GI cancer patients received S-1 chemotherapy. The key eligibility criteria are as follows: 1) Histologically confirmed carcinoma in GI cancer, including esophageal, gastric, colorectal, pancreatic, and biliary tract cancer.; 2) The patient who receives chemotherapy including S-1.; 3) No prior medication of S-1.; 4) No lachrymal duct obstruction and less than three points of corner conjunctiva epithelium disorder score. All participants receive four times of ophthalmological examinations. The primary endpoint is cumulative incidence of epiphora in periods from start of S-1 chemotherapy to 12 weeks after induction S-1. The secondary endpoints are cumulative incidence of epiphora in overall S-1 chemotherapy periods, the time of onset and severity of epiphora, the situation of ophthalmological intervention, ophthalmological changes, risk factors of epiphora, and QOL. Because we supposed that incidence of epiphora at 12 weeks after induction S-1 is 10% as already reported, we calculated the sample size as 160 based on precision of the 95% confidence interval and aimed to recruit 180 patients considering the possibility of 10% dropouts. This study is sponsored by Non Profit Organization Hokkaido Gastrointestinal Cancer Study Group.

Clinical trial identification: UMIN 000027192 24, June, 2017

Legal entity responsible for the study: Hokkaido Gastrointestinal Cancer Study Group

Funding: None

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1613TiP Outpatient monitoring with an eTool: self managed or with pro active intervention?

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Background: Cancer outpatients (OP) will face a maximum of potentially serious side effects (SAEI) and complications (C) at home and at distance from their caregivers (CG). This may lead to insufficent management as the care takers ignore complications and will not carry out early intervention. Worsening of quality of life (QoL) and (prolonged) hospitalisation may be the consequence. Studies have provided evidence that e-tools inquiring about the patients' well-being at home may be useful for early intervention, thus providing better quality of life and less hospitalisations. It is unclear whether these benefits could be obtained by patients' self-management or require pro active intervention (PAI) by CG. We therefore carry out a study (PRO-ELECTS= PE) using a web-based e-tool we developed based on the Edmondson Symptom Scale (ESAS). A pilot study had proved feasability in OU of the Oncology Outpatient Unit (OOU) of the CHEM general hospital.

Trial design: This prospective randomized study compares: - I. OP documenting QoL, hospital stays/consult. during treatment intervals while under OOU visits, with:- II. P receiving daily inquiries, automated advice and alerts to contact OOU in the case of SAE, with: III. P receiving daily inquiry superised by the OOU CG and intervention in case of alarming sypmtoms. All P apart from I receive daily customized questionnaires integrating an algorithm with automated answers to standard situations and alert messages inviting the P to contact the OOU tal in case of SAE. In group III, CG of the OOU will be notified of the daily response and alerted in case of SAE. They are mandated to contact the P to provide advice or convocate him to the hospital.PRO-ELECTS should be able to determine whether active electronic patient surveillance and pro active intervention is superior to patient self -management assisted by a web tool in maintaining good quality of life and limit the severity of complications. The study will also determine which strategy provideds more patient adherence and satisfaction. So far 15 of a total of 120 P have been randomized. Patient acceptance is excellent. 3 serious side effects have been anticipated through active intervention. Data concerning P adherence, satisfaction, QoL ad complication data will be presented.

Legal entity responsible for the study: Stefan Rauh

Funding: CHEM, Fondation Cancer Luxembourg, Integrated Biobank Luxembourg, CHEM, Janssen Cilag, Chugai

Disclosure: A. Hagemann: eHealth Consultant of the company Sananet providing the web site for the study All other authors have declared no conflicts of interest.

1614TiP A Phase I safety study of topical Calcitriol (BPM 31543) for the prevention of chemotherapy-induced alopecia (CIA)

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Background: Chemotherapy-induced alopecia (CIA) may lead to significant psychosocial and quality of life issues. Currently there are no FDA approved therapeutic agents available to prevent CIA. In murine studies, topical calcitriol reduced CIA, likely due to arrest of cell cycle in healthy hair follicles and reducing sensitivity of follicular epithelium to chemotherapy.

Trial design: A 3 + 3 dose-escalation Phase 1 study with 3 to 6 patients at each dose level (5/10/20/40/60/80 μg/mL) to determine the maximum tolerated dose (MTD) and the overall safety and tolerability of a topical compound BPM31543 (Calcitriol) in patients with a diagnosis of breast cancer, gynecologic cancer and sarcomas. Eligible patients receiving a taxane-based chemotherapy regimen applied 1mL of BPM31543 twice/daily at each cohort dose level 14 or 7 days prior to initiation of chemotherapy and then continued twice daily for 3 months or until termination of chemotherapy. In order to determine the MTD, dose escalation occurred in stepwise increments of the immediate prior dose group, in the absence of grade 3 or greater toxicities attributed to the topical calcitriol. Dose-limiting toxicity (DLT) was determined during Cycle 1 (i.e., the first 28 days of topical agent application). Patients were managed with adequate safety monitoring and pharmacokinetic (PK) analysis in order to determine levels of exposure. The potential efficacy (secondary objective) of the topical calcitriol was evaluated by photographic assessment using a Canon digital camera system (to ensure standardization and uniformity among all enrolled patients) in addition to patient self-assessments.

Clinical trial identification: NCT01588522

Legal entity responsible for the study: BERG, LLC

Funding: BERG, LLC

Disclosure: B. Berman, J. Konner, V.R. Belum, K. Ciccolini, S. Kitts, J.J. Jimenez, S.B. Goldfarb, M.E. Lacouture: Clinical investigator paid by BERG, LLC to conduct studies. H. Dion. R. Ye, S. Ravipaty, V.R. Akmaev: Employee of BERG, LLC and has stock options. R. Sarangarajan, N. Narain: Employee of BERG, LLC and has stock options, also a co-founder of BERG, LLC.

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THORACIC MALIGNANCIES, OTHER

1615O Pembrolizumab as second or further line treatment in relapsed malignant pleural mesothelioma: A Swiss registry

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Background: Available 2nd line chemotherapies for relapsed malignant pleural mesothelioma (MPM) have limited activity. Results from early clinical trials - including the mesothelioma cohort of the KEYNOTE-028 phase I/II trial - show promising activity of various PD-(L)1 checkpoint inhibitors in MPM. Pembrolizumab has been used off-label in Switzerland as 2nd and further line treatment in patients with MPM.

Methods: Cancer centers in Switzerland entered data on patients having received pembrolizumab for MPM into this retrospective registry. Patient characteristics including age, gender, histology, stage at diagnosis and previous treatments were collected. Outcomes of pembrolizumab were assessed by the local investigators using standard RECIST v1.1 criteria. PD-L1 expression was determined centrally.

Results: We collected data on 48 patients (median age 68 years) having received pembrolizumab for relapsed MPM between September 2015 and April 2017. Pembrolizumab was the 2nd line of treatment (after platinum-pemetrexed +/- bevacizumab) in 30 patients (63%). Twenty-eight patients (59%) had an ECOG of 0-1 at the beginning of pembrolizumab (as in the KEYNOTE-028 trial). Responses and survival outcomes are listed in Table. Investigator-reported toxicity was as follows: 15 treatment-related adverse events occurred in 14 patients (29%). Five events (10%) were G3-4 (2 patients with hepatitis, 1 with heart failure, 1 with non-cardiac chest pain and 1 with nephrotic syndrome). Seven patients (15%) discontinued treatment due to an adverse event.

Conclusions: This is the largest reported cohort of mesothelioma patients treated with pembrolizumab thus far, and the first with any kind of anti-PD(L)1 antibody in a "real-life" setting. Compared to available second-and-beyond line treatment options, response rates and survival outcomes were promising in the unselected population, while patients with ECOG 0-1 receiving pembrolizumab in 2nd line seemed to benefit substantially. Response rates as well as the incidence of treatment-related adverse events were consistent with the KEYNOTE-028 report. Further results including subgroup analysis by PD-L1 expression will be presented at the meeting.

Legal entity responsible for the study: Department of Oncology, Kantonsspital Graubünden, Chur

Funding: Krebsliga Graubünden, Chur, Switzerland

Disclosure: L.A. Mauti, H. Bouchaab, S.I. Rothschild, M. Pless, R. von Moos: MSD advisory board member.

U. Petrausch: Advisory board member for MSD.

S. Savic Prince: Spasenija Savic Prince has received speakers honoraria from MSD.

Y. Metaxas: MSD travel grant.

All other authors have declared no conflicts of interest.

1616O Multicenter, nonrandomized, open-label Phase 1b study of FP-1039/GSK3052230 with chemotherapy: results in malignant pleural mesothelioma (MPM)

J.M. Trigo Perez[1], E. van Brummelen[2], E. Levchenko[3], M. Domine Gomez[4], D.A. Fennell[5], H.L. Kindler[6], S. Viteri[7], S. Gadgeel[8], P. Garrido Lopez[9], V. Kostorov[10], D. Morgensztern[11], S. Orlov[12], P.K. Paik[13], J.F. Vansteenkiste[14], X. Wang[15], A. Sharabidze[15], M.P. Deyoung[15], K.P. Baker[16], L. Yan[15], I. Mitrica[15]

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Background: Fibroblast growth factor (FGF) signaling has a fundamental role in cancer development and tumor maintenance. FP-1039/GSK3052230 is a soluble decoy receptor that sequesters FGFs, including FGF2, blocking their ability to bind to and activate FGFRs, particularly FGFR1. This unique mechanism of action should avoid the on-target toxicities associated with small molecule pan FGFR kinase inhibitors, such as hyperphosphatemia and retinal, nail, and skin changes. MPM remains a disease with poor prognosis and few effective therapies, and preclinical models of MPM are particularly sensitive to inhibition of FGF/FGFR signaling by FP-1039/GSK3052230.

Methods: Herein, the analysis of patients with untreated, unresectable MPM is reported. The MPM arm of the study evaluated the safety and efficacy of FP-1039/GSK3052230 (IV weekly) in combination with standard pemetrexed+cisplatin. The study design involved dose escalation until MTD followed by a cohort expansion phase. Endpoints included safety, overall response rate by modified RECIST 1.1, disease control rate (DCR), PFS, and exploratory translational objectives.

Results: As of the cutoff date of 17 Mar 2017, 36 patients were dosed at 10, 15 and 20 mg/kg doses of FP-1039/GSK3052230. Three DLTs were observed at 20 mg/kg but none occurred at 15 mg/kg; therefore, MTD was declared at this dose. Most common related adverse events (all grades) were: nausea (56%) decreased appetite (36%), fatigue (33%), and infusion reaction (33%). The confirmed objective response rate (ORR) of all evaluable patients at or below the MTD was 48% (13/27 PRs), with disease control rate (DCR) of 100%. The median PFS was 7.4 months. As of 8 May 2017, six patients stayed on the study for over 1 year, of which 3 were still ongoing. Results of exploratory biomarker analyses will also be presented.

Conclusions: The MTD of FP-1039/GSK3052230 (15 mg/kg) in combination with pemetrexed+cisplatin in MPM was well tolerated, and durable responses were observed. Importantly, AEs associated with small-molecule pan FGFR kinase inhibitors were not observed, as predicted by the unique mechanism of action of this drug. Study sponsored by GSK; clinical trial information: NCT01868022.

Clinical trial identification: NCT01868022

Legal entity responsible for the study: GlaxoSmithKline

Funding: GlaxoSmithKline

Table: 1615O Outcomes

	total (n = 48)	ECOG 0-1 (n = 28)	ECOG 0-1 and 2nd line Pembro (n = 19)
ORR	25% (1 CR + 11 PR)	32% (1 CR + 8 PR)	42% (1 CR + 7 PR)
DCR	52% (incl. 13 SD)	57% (incl. 7 SD)	74% (incl. 6 SD)
mPFS (95% CI), months	3.2 (2.6 - 4.8)	3.7 (2.8 - 6.7)	5.3 (3.6 - NR)
mOS (95% CI), months	7.9 (6.2 - NR)	9.3 (6.8 - NR)	NR (8.2 - NR)
alive at 6 months (95% CI)	65% (52 - 81%)	72% (56 - 92%)	77% (59 - 99%)
alive at 12 months (95% CI)	28% (15 - 53%)	43% (24 - 77%)	52% (29 - 95%)

Disclosure: D.A. Fennell: Advisory Board/consultant – Astra Zeneca, BMS, Bayer, Boehringer Ingelheim, Clovis, Roche, Eli Lilly, MSD H.L. Kindler: Advisor: Aduro; AZ; Bayer; Celgene; Genentech/Roche; Gilead; GSK; MedImmune; Merck; Plexxikon; Verastem. Grants: AB Science; Aduro; Astellas Pharma; AZ; Bayer; Celgene; GSK; Incyte; MedImmune; Merck; Verastem. Expert Testimony: Aduro S. Viteri: Grants: AbbVie, ARIAD, Astex, AZ, BI, Clovis, CytRx, Daiichi Sankyo, GSK, Hanmi, Incyte, Merck KGaA, Novartis, Pfizer, Puma, Roche, Servier, Vaxon. Advisor: BI, Clovis, Idea Pharma, Novartis, Promega Biotech Ibérica, Roche, Targovax S. Gadgeel: Advisor/Board member: Genentech/Roche, Pfizer, Ariad, Astra-Zeneca Speakers bureau: Genetech/Roche, Astra-Zeneca Travel Compensation: Genentech/Roche P. Garrido Lopez: Advisor/Board member: MSD, Pfizer, BMS, Novartis, Roche, BI, Guardant Speakers bureau: MSD, Pfizer, BMS, Novartis, Roche Honorarium recipient: BI D. Morgensztern: Advisor/Board member: Abbvie, Celgene, Bristo-Myers Squibb J.F. Vansteenkiste: Grants/research support recipient: AZ Honorarium/consulting: AZ, Novartis, MSD, BI, Eli-Lilly, Roche X. Wang: Full-time employee with GlaxoSmithkline A. Sharabidze: Consultant at GSK M.P. Deyoung: Full time employee and stock owner of GSK K.P. Baker: Full time employee of Five Prime Therapeutics L. Yan, I. Mitrica: Full time employee of GSK and stock owner All other authors have declared no conflicts of interest.

1617PD Multiplexed targeted proteomics signature for serum diagnostic of malignant pleural mesothelioma

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Background: Detection of mesothelioma from blood is challenging. Current proposed biomarkers mainly rely on single protein cancer products detected in serum or plasma. Here, we investigate if a mass spectrometry based multiplexed proteomic biomarker signature can improve accuracy of mesothelioma detection in serum.

Methods: We used targeted proteomics technology to investigate more than 400 serum samples from cohorts of mesothelioma and asbestos exposed donors from USA, Australia and Europe. Serum samples were processed for enrichment of N-linked glycoproteins on 96-well plates before peptide separation on ultra performance liquid chromatography (UPLC) followed by targeted analysis on a triple quadrupole type of mass spectrometer. The software Skyline was used for data visualization. Workflow for quantitative large scale data analysis was based on the software package MSstats.

Results: We applied logistic regression models for a multiplexed signature of six peptides from six different proteins, including the biomarker mesothelin. In the receiver operating curve, signature had an area under the curve (AUC) of 0.76 in discriminating mesothelioma from asbestos exposed donors in a training set of 212 donors. AUC in a separated validation set of 193 donors was 0.72. In the validation set, AUC was 0.74 in separating mesothelioma early stages I/II from asbestos exposed. In comparison, single mesothelin peptide assessed by mass spectrometry discriminated mesothelioma from asbestos exposed with AUC of 0.71 in training and AUC of 0.64 in validation set, and mesothelioma early stages I/II were separated from asbestos exposed with AUC of 0.66 in the validation set.

Conclusions: Diagnostic strategies based on multiplexed targeted proteomics biomarkers bear potential of an increased accuracy for detection of mesothelioma in serum.

Legal entity responsible for the study: James Thoracic Center, The Ohio State University Medical Center

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1618PD Overall survival (OS) and forced vital capacity (FVC) results from the LUME-Meso study of nintedanib (N) + pemetrexed/cisplatin (PEM/CIS) vs placebo (P) + PEM/CIS in chemo-naïve patients (pts) with malignant pleural mesothelioma (MPM)

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Background: N targets MPM by inhibiting VEGFR 1–3, PDGFR α/β, FGFR 1–3, Src and Abl kinases. In a Phase II/III, double-blind, randomised LUME-Meso trial, primary Phase II analysis showed improved progression-free survival (PFS) with N and a trend for prolonged interim OS. FVC, a common pulmonary function test reflecting pt performance and quality-of-life, was also evaluated.

Methods: Pts with unresectable MPM (ECOG PS 0–1), stratified by histology, were randomised 1:1 to ≤ 6 cycles PEM (500 mg/m^2)/CIS (75 mg/m^2, Day 1) + N or P (200 mg bid, Days 2–21), followed by N/P monotherapy until progression/unacceptable toxicity. The primary endpoint was PFS; OS was the secondary endpoint. FVC was a further endpoint, evaluated as percentage change from baseline for cycle (C)1–8 using a mixed-effect model with repeated measures.

Results: 87 pts were randomised (N = 44; P = 43). At the primary OS analysis (71% of events), OS benefit favoured N (hazard ratio [HR]=0.77; 95% confidence interval [CI]: 0.46–1.29; p = 0.319) and primary PFS results were confirmed (HR = 0.54; [95% CI]: 0.33–0.87; p = 0.010). Benefit of N was greatest in epithelioid MPM for PFS (HR = 0.49; 95% CI: 0.30–0.82; p = 0.006; median [m] 9.7 vs 5.7 months [mo]) and OS (HR = 0.70; 95% CI: 0.40–1.21; p = 0.197; mOS 20.6 vs 15.2 mo). Adjusted mean (standard error [SE]) FVC change at C8 favoured N over P (all pts: +10.0 [SE: 3.5]% vs + 2.8 [SE: 3.7]%; mean treatment difference [TD]: 7.2 [SE: 4.5]%; pts with epithelioid histology: +14.1 [SE: 2.9]% vs + 4.2 [SE: 3.3]%; mean TD: 9.9 [SE 4.5]%). A trend towards improved FVC with N over P was observed from C2 in all pts and epithelioid histology. Neutropenia was the most frequent Grade ≥3 adverse event (AE; N, 43%; P, 12%); febrile neutropenia rate was low (4.5 vs 0%). AEs leading to discontinuation were lower with N than P (7 vs 17%).

Conclusions: Addition of N to PEM/CIS resulted in a substantial improvement in PFS, a trend for prolonged OS and improvement in the pulmonary function measure FVC. Treatment effect was most pronounced in pts with epithelioid histology; Phase III is recruiting in this population (NCT01907100).

Clinical trial identification: NCT01907100

Legal entity responsible for the study: Boehringer Ingelheim Pharma GmbH & Co. KG

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1619PD Malignant pleural mesothelioma immune microenvironment and checkpoint expression before and after systemic cytotoxic treatment

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Background: Tumor immune microenvironment (TME) plays a role in Malignant Pleural Mesothelioma (MPM) pathogenesis and patients outcome. PD1/PDL1 checkpoint inhibitors are currently under investigation as innovative promising treatment of MPM, even though no definitive predictive markers have been defined so far. PDL1 expression and TME are dynamic in tumor samples. The object of this preliminary analysis is a subset of MPM paired samples analyzed before and after induction chemotherapy (ct) in order to assess TME and PDL1 heterogeneity and dynamism over time.

Methods: Inflammatory cells in the intratumoral (IT) e peritumoral (PT) stroma were characterized by immunohistochemistry (IHC) using monoclonal anti-CD20 (B lymphocytes), CD3, CD4 and CD8 (T lymphocytes) and CD68 (macrophages) antibodies, and quantified as percentage in neoplastic area. PDL1 expression in tumor cells (TC) and immune cells (IC) was evaluated by IHC using Ventana SP263 antibody (Roche) and quantified as percentage of expressing cells. Difference between naïve and treated samples was assessed through Mann-Whithey test.

Results: 15 paired MPM specimens (14 epithelioid and 1 biphasic) obtained for diagnostic purpose before platinum-pemetrexed ct and at the time of resection were analyzed. After ct MPM samples showed PT and IT increase of CD68+ macrophages and CD3+ T lymphocytes, even though only peritumoral CD3+ lymphocytes significantly increased (p=0.008). CD4+ and CD8+ lymphocytes were lacking in naive samples, while CD8+ significantly increased after ct (median value PT pre *vs.* post-ct: 5% *vs.* 30%, p=0.02; median valule IT pre *vs.* post-ct: 5% *vs.* 15%, p= 0.007). CD8+/CD68+ ratio increased after ct, even though without statistical significance. No IT B lymphocytes were observed, a small increase at PT level was shown after ct. Ct induced PDL1 expression in tumor cells and even more in lymphomonocitic infiltrate (median value pre *vs.* post-ct 0% *vs.* 50%, p=0.003).

Conclusions: Ct significantly increases cytotoxic T lymphocytes at PT and IT level in MPM samples and PDL1 expression in IC. These data confirm the strong rationale for the combination of checkpoint inhibitors and ct as promising treatment of MPM.

Legal entity responsible for the study: Istituto Oncologico Veneto IRCCS

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Disclosure: All authors have declared no conflicts of interest.

1620P Outcomes of malignant pleural mesothelioma (MPM) patients (p) treated with immune-oncology drugs (IO) in clinical trials

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Background: The increasing incidence and poor outcome associated with MPM requires identification of effective treatment options. Initial data have demonstrated beneficial effects of IO in MPM, however recent results of clinical studies with immune checkpoint inhibitors (CPI) are not so encouraging. The aim of this study is to evaluate the outcomes of p with MPM treated with immunotherapy in clinical trials at our institution.

Methods: 20 MPM p treated with IO at Vall dHebron Institute of Oncology between September 2012 and December 2016 were reviewed. Survival data were calculated by the Kaplan-Meier method. The associations of type of immunotherapy with outcomes were assessed with Cox regression models.

Results: Patient's characteristics: median age 63 years (45-77 years), males: 62%, performance status (PS) 1:86%, asbestos exposure: 82%, stage III at diagnosis: 51%, epithelial subtype: 82%. All p were treated with chemotherapy, 90% received cisplatin plus pemetrexed as first line with median progression free survival (PFS) of 9.1 months (m;CI95% 7.6-10.7). Clinical trial with IO was offered as second-line regimen in 65% and third line in 35%. Target of IO was CTLA4: 60%, PD-1: 25% and other CPI single agent 15% (LAG3, GITR, CD40). Overall, disease control rate at 4 months was 40%. Reason for treatment discontinuation was toxicity in 20% of cases. Median PFS with IO in second line was 5.6 m (2.7-NR) and in third line 3.7 m (1.4-NR, $p = 0.77$). Different outcomes were seen according to target selected: with PD-1 median PFS of 8.6 m (4.2-NR) and with CTLA4 of 4.2 m (2.2-NR), significantly longer than 1.9 m (0.7-NR) with other CPI ($p < 0.05$). Overall, median survival (OS) was 26.9 m (21.8-NR). Survival after initiation of IO was 9.6 m (7.2-NR) if given in second-line and 4.9 m (4.5-NR) in third line ($p = 0.67$). Baseline and dynamic changes in LDH and lymphocytes were not predictors of outcomes to immunotherapy ($p > 0.05$ all comparisons).

Conclusions: In our single institution series of previously treated MPM, IO associates with prolonged disease control in a subgroup of patients, with longest benefit seen with anti PD-1 therapies. Further research with predictive biomarkers of IO in MPM is needed.

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1621P Baseline hyperglycemia was predictive of poor outcome in pleural malignant mesothelioma

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Background: Although numerous prognostic biomarkers were described in malignant pleural mesothelioma (MPM), the role of hyperglycemia has not been studied. We examined reported prognostic variables and glycemia as predictors of overall survival (OS) in a cohort of MPM patients.

Methods: This retrospective study included 148 consecutive patients diagnosed with MPM in two hospitals from Catalonia between 2007 and 2016. Clinicopathological characteristics and baseline analytical results were recorded. OS was calculated using Kaplan-Meier method and multivariate Cox model was adjusted by clinical variables that were statistically significant in the univariate Cox regression.

Results: Most patients were male (73%) and 56% were $\geq$ 70 years. The most frequent histological subtype was epithelioid (59.5%), followed by sarcomatoid (18%), biphasic (13.5%) and not specified (10%). Disease stages at diagnosis were: stage I, 11.5%; stage II, 16%; stage III, 33%; stage IV, 34%; not specified, 1.5%. Most patients had good ECOG performance status (PS 0-1, 63%) and 63% of patients received chemotherapy. Median baseline glycemia was 5.8 mmol/l (3.9-15.9) and patients 34 (23%) had hyperglycemia ($\geq$7 mmol/l) and 26 (18%) previous diagnosis of diabetes. The median overall survival (OS) was 10.5 months (95% CI 7.6 – 13.4). In the univariate analysis for OS, histological subtype, stage, PS, chemotherapy treatment, hyperglycemia ($\geq$7 mmol/l), high neutrophil and platelets count, low lymphocytes and and high neutrophil to lymphocyte ratio (NLR) were significantly associated with survival outcome. In the multivariate Cox model adjusted by histological subtype, stage and PS, baseline glycemia (HR 1.80, 95% CI 1.08-2.98, $p = 0.023$, Table) and neutrophil count (HR 1.42, 95% CI 1.01-1.98, $p = 0.042$) remained as independent prognostic factors for shorter OS.

Table: 1621P Multivariate Cox Regression Analysis of Overall Survival

	HR (95% CI)	p-value
Histology (non-epithelioid vs. epithelioid)	2.16 (1.42 - 3.26)	**<0.001**
Stage, continuous	1.28 (1.04 - 1.56)	**0.017**
ECOG PS, continuous	1.82 (1.42 - 2.32)	**<0.001**
Baseline glycemia, continuous	1.80 (1.08 - 2.98)	**0.023**

Conclusions: Baseline hyperglycemia was independently associated with shorter survival in this cohort of patients with MPM. Confirmation of its prognostic role in larger cohorts is warranted.

Legal entity responsible for the study: Catalan Institute of Oncology

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Disclosure: All authors have declared no conflicts of interest.

1622P Evaluation of quality of life in survivors with malignant pleural mesothelioma in Japan

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Background: Malignant pleural mesothelioma (MPM) is the malignancy with poor prognosis. Most patients with MPM present severe symptoms such as pain, dyspnea and fatigue. Because of the symptoms and poor prognosis, MPM survivors would have poor Quality of Life (QOL), however, their QOL has not been well evaluated.

Methods: Subjects were the survivors of MPM. We asked the cancer hospitals in Japan and MPM Patients' Association to distribute the self-administered questionnaire. QOL was evaluated using scales of the EORTC QLQ-C30 and QoQoLo short version. In addition to the QOL, clinical factors were collected using the questionnaire. Mean and its standard deviation were used to evaluate QOL scores. Wilcoxon rank sum test was used to compare the QOL scores. Factors affecting the QOL score were evaluated by multiple regression model.

Results: In total, 133 survivors with MPM participated in the study. Regarding the QOL evaluated by QLQ-C30: functional scales were poor (scores >50), while symptom scales were not so poor (scores <50). When stratified by performance status (PS), functional scores were worse in survivors with good PS than those with poor PS, while symptom scales were better in good PS survivors than those with poor PS. CoQoLo scale showed MPM survivors had good relationships with their doctors, whereas, they suffered from physical and psychological pain, and had the feeling to be a burden to others. Global health status score evaluated by QLQ-C30 were significantly better among survivors with good PS, >2 years from diagnosis, and female. Similarly, good PS and >2 years from diagnosis were the factors caused higher total score of CoQoLo core domein.

Conclusions: Survivors with MPM had physical and psychological difficulties. Even the survivors with good PS had functional difficulty. Individualized supports are required for survivors with MPM.

Legal entity responsible for the study: Nobukazu Fujimoto

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Disclosure: All authors have declared no conflicts of interest.

1623P Staging and assessment of the response to PET-CT treatment in non-small cell lung carcinoma

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Background: Non-small cell lung cancer (NSCLC) is the leading cause of death from tumors in Western countries. Mediastinal involvement is the most important factor to determine treatment and prognosis. The aim of this study was to analyze the concordance between histological mediastinal staging with that demonstrated by positron emission tomography and computed tomography (PET-CT), in addition to defining the characteristics of this population.

Methods: We prospectively evaluated 244 patients diagnosed with NSCLC at Puerta de Hierro Hospital, from 2009 to 2016. Mediastinal staging was determined by imaging (CT and PET- CT) and anatomo-pathological examination (endobronchial ultrasound, mediastinoscopy or lymphadenectomy). Variables collected included tumor size by CT and PET- CT, lymph node involvement, treatment, and survival. The findings of PET-CT were compared with the histological findings to determine the sensitivity, specificity, and positive (PPV) and negative (NPV) predictive values.

Results: Median of age was 66 years, 74% patients were male,22% were non-smokers. Most common histologies were adenocarcinoma (45%) and squamous (37%). 12% patients presented EGFR mutations (64% 19del) and 3%were ALK-translocated. Staging results by PET-CT were: I (26%), II (21%), III (A 26% and B 14%) and IV (10%).

The correlation in staging between CT and PET-CT, obtaining a kappa index of 0.9 ($p < 0.0001$)(Landis and Koch κ values: almost perfect agreement). In stages I and II the correlation between PET-CT and final outcome after surgery was0.61 ($p < 0.0001$)(κ values: substantial agreement). For mediastinal assessment, PET- CT has a sensitivity of 85% and specificity of 45%, PPV 61% and NPV 74%.

Conclusions: According to the data observed in our series, there is a strong concordance between the two radiological tests for staging of NSCLC (PET-CT and CT). There is also agreement between PET-CT and subsequent pathological findings in NSCLC in initial stages (I and II). Because of the high sensitivity and NPV of the PET-CT for mediastinal staging, a positive result of this test requires an histological correlation.The increase in the use of PET- CT contributes to more accurate selection of patients for appropriate treatment.

Legal entity responsible for the study: Puerta de Hierro University Hospital

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1624P "Liquid Withdarw" technique prominently reduced the incidence of pneumothorax and improved tumor tissue amount of CT-guided cutting needle lung biopsy: A retrospective study

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Background: CT-guided cutting needle lung biopsy is important for the diagnosis of lung cancer. In the area of precision medicine, it has become important to obtain adequate tumor tissue for the molecular testing. Pneumothorax is one of the most prevalent complications of the biopsy. In previous study, we found that "liquid withdraw" technique (to inject small amount of liquid durimng the withdrawal of the needle) can prominently reduce the incidence of pneumothorax. In this report, we retrospectively studied 92 CT-guided lung biopsy to investigate the role of this technique in reducing complications and promoting biopsy effevtiveness.

Methods: From Jan 1st, 2014 to Nov 30th, 2016, we retrospectively studied 92 CT-guided lung biopsy using liquid withdraw techniques in 90 patients. The pathologies (cytology, histology and EGFR mutation status) and complications secondary to biopsy procedure (pneumothorax, bleeding, etc.) were noted. Pneumothorax and bleeding was graded as mild (mild and very mild), moderate, and severe.

Results: 88 cases were diagnosed out of 92 biopsies (95.7%), of which 60 cases were adenocarcinoma. Among 52 cases of adenocarcinoma who consented EGFR mutation test, only 1 case (1.9%) was failed due to insufficient tissue. Among all the biopsies, when cutting tumor tissue 4-6 times per procedure, the incidence of pneumothorax was in 18 cases (19.6%), among which 13 cases (14.1%) were very mild pneumothorax (lung surface retraction of ≤ 1 cm), mild and moderate pneumothorax accounted for just 4.3%. No severe pneumothorax occurred. No other severe complications happened.

Conclusions: Compared to lung biopsy without liquid withdraw, the incidence of pneumothorax using "liquid withdraw technique" was reduced from approximately 35% to 19.6% (14.1% were very mild pneumothorax and 0% were severe pneumothorax). The liquid withdraw technique also resulted in low rate of other complications and adequate tissue for diagnosis and treatment planning of lung cancer. Next, we are planning to conduct a prospective study to further evaluate the role of liquid withdraw technique in the precision diagnosis and treatment of lung cancer.

Legal entity responsible for the study: The Comprehensive Cancer Center of Drum-Tower Hospital, Medical School of Nanjing University

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Disclosure: All authors have declared no conflicts of interest.

1625P Phase II trial of S-1 treatment as palliative-intent chemotherapy for previously treated advanced thymic carcinoma

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Background: Thymic carcinoma (TC) is a rare cancer with minimal evidence of survival with palliative-intent chemotherapy. Sunitinib and everolimus monotherapies have been proposed as active molecular-targeted approaches based on phase II (Ph II) trials, and S-1, an oral fluoropyrimidine, has been described in the NCCN guideline as an active cytotoxic agent for refractory TC based on a case series. Therefore, we conducted a Ph II trial to study the result of S-1 treatment in patients with refractory TC.

Methods: In this Ph II study performed at three cancer centers in Tokyo, we aimed to enroll 26 TC patients previously treated with platinum-based chemotherapy. The patients received S-1 orally twice daily at a dose of 40–60 mg/m^2 for 4 weeks, followed by 2 weeks off until progressive disease or unacceptable toxicities. S-1 was used off-label. The primary end-point was determining the objective response rate, and secondary endpoints were progression-free survival (PFS), overall survival (OS), and toxicities.

Results: Twenty-six patients (10 males) were recruited between November 2013 and May 2016. The median age was 63 (27–74) years. Among the 26 patients, 23 had squamous cell carcinoma histology and 10 had an ECOG performance status of 0. Additionally, one patient showed complete response and seven patients showed partial responses, resulting in a 30.8% response rate (95% confidence interval [CI], 16.5–50.0) and a 65.4% disease control rate (95% CI, 46.2–80.6). After a median follow-up of 13.4 months, the median PFS was 4.3 months (95% CI, 2.3–7.6 months) and median OS was 23.4 months (95% CI, 12.8–not reached). Treatment-related adverse events (AEs) of grade $\geq$3 included neutropenia (12%), skin rash (8%), elevated ALT, decreased WBC count, and fatigue (4%). No treatment-related death was observed. However, treatment was discontinued in three patients (12%) because of AEs.

Conclusions: S-1 as palliative-intent chemotherapy and a cytotoxic agent for refractory TC confirmed clinical activity with good tolerability.

Clinical trial identification: UMIN000010736

Legal entity responsible for the study: /National Cancer Center Hospital/The Cancer Institute Hospital of Japanese Foundation for Cancer Research/Tokyo Metropolitan Cancer and Infectious diseases Center Komagome Hospital

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1626P Detects esophageal squamous cell carcinoma via liquid biopsy of circulating exosomes

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Background: As with many cancers, survival rates for esophageal squamous cell carcinoma (ESCC) are poor when the disease is diagnosed at a later stage whitout any symptoms. Exosomes are 40-150nm small vesicles in blood and other body fluids and have been described as promoters of tumor progression. Although the secretory mechanisms of tumour-associated exosomes are still unclear, the use of circulating exosomes as potential non-invasive biomarkers might become promising. The object of this stduy was to determine whether the circulating exosomes can serve as biomarkers in ESCC.

Methods: Serum samples were obtained from 100 patients with ESCC and 100 healthy volunteers. Exosomes were extracted by Total Exosome Isolation Reagent, and purified to selectively capture tumor-asscociated epithelial cell adhesion molecule (EpCAM) positive exosomes by magnetic-bead technique. ELISA was performed to measure the expression of CD9 protein. Cell invasion was measured using transwell chamber. Expression levels were compared by using the Mann-Whitney U test, Friedman or Wilcoxon test., Receiver-operating characteristics (ROC) curve was established to evaluate the diagnostic value of exosome for the differentiation between ESCC patients and controls. Univariate analysis of OS and DFS was performedas outlined by Kaplan-Meier test.

Results: Expression levels of exosomal CD9 were significantly higher in ESCC patients than in healthy individuals ($p < 0.05$). The expression levels of exosomal CD9 in different TNM stages and grades were significantly higher than in the controls ($p < 0.05$, respectively). ROC analysis demonstrated that expression levels of exosomal CD9 distinguished patients with ESCC from healthy individuals with 76% sensitivity and 84% specificity. Kaplan-Meier analysis demonstrated that increased expression of exosomal CD9 was associated with poor OS and PFS in ESCC patients ($P < 0.05$). In addition, the experiments of delayed processing, freezing and thawing did not affect the expression levels of exosomal CD9. Transwell and wound scratching assay showed that the exosomes could promote cell invasion and migration.

Conclusions: Serum exosomal CD9 might represent potential diagnostic and pronostic biomarkers in ESCC in the future.

Legal entity responsible for the study: Zhejiang Cancer Hospital

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Disclosure: All authors have declared no conflicts of interest.

1627TiP ONCOS-102 and pemetrexed/cisplatin in patients with unresectable malignant pleural mesothelioma

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Background: Mesothelioma is a rare cancer with poor prognosis and limited treatment options, including surgery, radiotherapy and chemo (pemetrexed + cisplatin/carboplatin). Adenoviruses are excellent immunotherapeutic agents with a unique ability to prime and boost immune responses. ONCOS-102 is a granulocyte-macrophage colony stimulating factor (GM-CSF) – expressing oncolytic adenovirus (Ad5/3-D24-GMCSF). In a prior phase I study of 12 patients (pts) with advanced solid tumors, 40% had stable disease (SD) at 3 months, 11/12 pts had infiltration of CD8+ lymphocytes in lesions, and 10/12 had intralesional PD-L1 expression increase. Lesional immune activation was seen in two pts with mesothelioma.

Trial design: A randomized Phase II study (n = 24) with a non-randomized Phase Ib safety lead-in cohort (n = 6). The study will compare ONCOS-102 and chemo with chemo alone (control arm). Eligible pts have histologically confirmed unresectable disease and are not candidates for curative surgery. Pts can be naïve to chemo, or have received and responded to chemo, but relapsed after at least 6 months thus eligible for renewed chemo treatment. Pts must have measurable disease with tumour accessible to intratumoural injections of ONCOS-102 and biopsies. A Data Safety Monitoring Committee will review data when the first 3 and all 6 pts have completed the Day 64 visit (i.e. after 2 cycles of chemo and 4 injections of ONCOS-102). If safety is acceptable, phase II will start with 10 pts in the control arm, and 14 pts in the experimental arm. Primary objective: Safety. Secondary objectives: 1) Tumour specific immunological activation in peripheral blood and biopsies 2) Response Rate 3) Progression Free Survival 4) Overall Survival and 5) Correlation between immune activation and clinical outcome. Treatment: Single cyclophosphamide dose followed by intratumoral injection of ONCOS-102 at 3x10^{11}viral particles (VPs) on days 1, 4, 8, 36, 78 and 120. Pemetrexed (500mg/m^2)/cisplatin(75mg/m^2) is given on day 22 and every 3 weeks for a maximum of 6 cycles. Imaging at baseline, Day 64 and 148. Tumor biopsies from both injected and non-injected lesions at baseline and Day 36.

Clinical trial identification: Eudra CT: 2015-005143-13 ClinicalTrials.gov. NCT02879669

Legal entity responsible for the study: Targovax OY, Helsinki, Finland

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ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

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TRANSLATIONAL RESEARCH

1628O Development of the Manchester Cancer Research Centre Molecular Tumour Board for matching patients to clinical trials based on tumour and ctDNA genetic profiling

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Background: Advances in Next Generation Sequencing (NGS) are enabling detailed molecular analysis of tumour and circulating tumour DNA (ctDNA). Combined with the expanding development of targeted therapies we are in the era of Precision Medicine. Molecular Tumour Boards (MTB) are needed to interpret genomic data and inform on clinically relevant matched therapies. We describe our experience of setting up a MTB to deliver a world-class genomic driven oncology programme.

Methods: Patients referred to the Experimental Cancer Medicine Team were consented for analysis of ctDNA and tumour under the TARGET (Tumour ChAracterisation to Guide Experimental Targeted Therapy) protocol. ctDNA was subjected to NGS and bioinformatic analysis for alterations in 650 cancer associated genes. Tumour was analysed by NGS for a panel of 24 genes regarded as relevant for treatment of solid tumours. We established a MTB comprising medical oncologists, clinical geneticists, bioinformaticians, scientists and bioethicists to interpret results and advise on clinical relevance and trial options. The aim of Part A of TARGET was to establish workflow and process.

Results: From Apr 2015 to Nov 2016 we recruited 100 patients to Part A. Main tumour types were colorectal (24%), breast (20%) and lung (18%). In 41% of patients a potentially actionable aberration was identified. The main challenges were i) optimisation of a bioinformatic pipeline for ctDNA, ii) linking clinical data with genomic data in a single portal, iii) interpretation of unknown variants and iv) linking results to available clinical trials in UK/Europe.

Conclusions: We have successfully implemented a comprehensive molecular profiling programme. The bioinformatic pipeline for ctDNA has evolved through real-life data collection and comparison with tumour/germline DNA. We are developing a web-based interface for linking clinical and genomic data for visualisation and annotation within the MTB. Variant interpretation software packages are being evaluated for data curation and ability to link with matched clinical trials. Recruitment of 450 patients to Part B of TARGET is underway to match patients with early phase trials in real-time.

Clinical trial identification: CFTSp094

Legal entity responsible for the study: Study sponsor is The Christie NHS Foundation Trust

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1629O A systematic rapid autopsy program tracks temporal and spatial heterogeneity of human tumors and identifies mechanisms of resistance to targeted therapies

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Background: Temporal and spatial heterogeneity of human tumors pose a significant barrier in the identification of effective anticancer therapies. Rapid autopsy, defined as post-mortem examination with collection of tissues for diagnosis and research within 6 hours of death, is a critical tool offering insight into this phenomenon.

Methods: Since January 2014, an on-call rapid autopsy team consisting of a pathologist, medical oncologist, pathology assistant and a tissue collection coordinator performed rapid autopsies on 51 patients with genomically-defined advanced solid tumors. Samples were collected from the primary tumor when present, multiple metastatic lesions, blood, as well as multiple uninvolved sites. All samples were recorded in a centralized database linked to patient's treatment history, as well as all previously collected tissue and liquid biopsies, under one clinical data and sample collection protocol. Samples meeting minimum viability and tumor cellularity criteria were selected for downstream analyses, including next-generation sequencing and protein-based assays.

Results: In 51 rapid autopsies, a median of 12 tissue samples were collected per autopsy (range 5-24), after a median of 2 hours and 50 minutes post mortem (range 32 minutes - 9 hours). 47 autopsies (92.2%) were completed $<$ 6 hours post mortem, and 4 autopsies (7.8%) were completed $>$ 6 hours post mortem due to delays in the confirmation of the autopsy consent from the patient's healthcare proxy and transportation delays. Tumor cellularity of collected samples ranged from 0-90% (median 60%), making these samples highly suitable for subsequent genomic analyses. Full analysis of 3 autopsy series revealed molecular alterations driving resistance to PI3K-alpha inhibitors, CDK4/6 inhibitors and FGFR inhibitors in patients with PIK3CA-altered metastatic breast cancer and FGFR2 fusion positive cholangiocarcinoma.

Conclusions: Rapid autopsies complement serially collected tissue and liquid biopsies, providing invaluable samples for analysis of tumor heterogeneity, evolutionary dynamics and determination of resistance mechanisms to targeted therapies.

Legal entity responsible for the study: Dejan Juric

Funding: Susan Eid Tumor Heterogeneity Initiative

Disclosure: All authors have declared no conflicts of interest.

1630PD Association of programmed cell death 1 ligand (PD-L1) expression with molecular alterations in non-small cell lung cancer (NSCLC) patients (pts): Results from the European Thoracic Oncology Platform (ETOP) Lungscape cohort

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Background: PD-L1 is the only validated predictive biomarker for use with immune checkpoint inhibitors targeting the PD-1 pathway in advanced NSCLC.

Methods: Correlation of PD-L1 expression with that of MET, ALK, PTEN proteins by IHC (MET+:$\geq$2+ and % staining$\geq$50%, ALK+: $\geq$1+, PTEN+: H-score$>$0) and mutations in *KRAS*, *EGFR*, *PIK3CA* or *MET* genes was explored in the large international ETOP Lungscape cohort of resected, stages I–III, NSCLC. The DAKO 28-8 immunohistochemistry assay was used to assess PD-L1 expression, and gene mutations testing was based on Fluidigm technology, a microfluidics-based multiplex PCR platform. PD-L1 expression was defined with alternative cut-offs ($\geq$1%, 5%, 50%) for neoplastic cell membrane staining.

Results: PD-L1 expression was assessed in 2182 pts, from 15 centers, 51/42/7% adenocarcinomas (AC)/squamous cell carcinoma (SCC)/other, 49/29/22% stage I/II/III, 32/54/11% current/former/never smokers, 4% unknown smoking status. For the 1% cut-off, a significant association was detected between PD-L1 and MET expression both for AC and SCC (PD-L1 positivity in AC: 61% in MET + vs 33% in MET-, $p < 0.001$; SCC: 57% vs 42%, $p = 0.005$). PD-L1 positivity was more frequent in PTEN expressing AC (48% vs 37% in PTEN loss subgroup, $p = 0.0017$), but not in SCC ($p = 0.62$). The association of ALK expression and PD-L1, explored only in the AC, was not significant ($p = 0.42$). Significant associations were also detected in AC between PD-L1 and *KRAS*

and *EGFR* genes. PD-L1 positivity was higher in *KRAS* mutated pts (AC: 46% vs 38% in KRAS wild-type (wt), p = 0.022; SCC: p = 0.88), and less frequent in *EGFR* mutated pts (AC: 27% vs 42% in EGFR wt; p = 0.012; SCC: only 8 mutated pts, no inference can be drawn). No significant correlation was detected between PD-L1 and *PIK3CA* or *MET* mutations. Results were analogous for the 5% and 50% cut-offs, with the exception of non-significant association between PD-L1 and *EGFR* in AC.

Conclusions: In this large NSCLC cohort, PD-L1 positivity (with 1%, 5% or 50% cut-off) is found to be significantly associated with IHC MET overexpression, expression of PTEN and *KRAS* mutation.

Legal entity responsible for the study: European Thoracic Oncology Platform (ETOP)

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1631PD Prominent immune suppressive tumor microenvironment in female never-smoker lung cancer patients with EGFR mutations

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Background: According to genetic and genomic analysis as well as previous clinical research, lung cancer in never-smokers might have pathogenesis and progression different from that of lung cancer among smokers. There has been indirect evidence that different types of mutations in tumors might be related to the altered immune functions.

Methods: Tissues from 110 female patients with lung adenocarcinoma (never-smokers: 102 & smokers: 8) at the Samsung Medical Center, were analyzed by next-generation genomic sequencing including whole-exome seq and RNA-seq. Somatic mutations and gene expression levels of immune signature genes were profiled. The significance for clinical outcome of the selected genes was plotted using Kaplan-Meier method and log-rank test.

Results: Expression biomarkers of immune suppressive cells such as mast cells, macrophage and Treg were prominent in female never-smokers compared to female smokers of lung adenocarcinoma. The data suggest that cells of cytotoxic functions are deactivated in smokers, whereas cells of immune suppressive functions are activated in never-smokers. Specifically as expression of immune markers specific for B-cells, dendritic cells, mast cells and Treg was especially up-regulated ($p<.05$) in tumors from patients with EGFR mutation (42%), its mutation status may play an important role in augmenting the immune suppressive activity. EGFR mutation–positive adenocarcinoma was significantly associated with low level of expression of an immune checkpoint molecule, programmed death-ligand 1 (PD-L1), in contrast with high level of cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) in female never-smokers.

Conclusions: This overall immune suppression in lung adenocarcinoma patients with EGFR mutation might explain the lower response rate of anti-PD-1/PD-L1 blockade to the female never smokers, which suggests that other approaches to block the immune suppressive microenvironment would be necessary.

Legal entity responsible for the study: The Institutional Review Board of Samsung Medical Center

Funding: Samsung Cancer Research Institute

Disclosure: All authors have declared no conflicts of interest.

1632PD A novel radiomic based imaging tool to monitor tumor lymphocyte infiltration and outcome of patients treated by anti-PD-1/PD-L1

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Background: Tumor infiltrating lymphocytes (TIL) appears necessary to trigger anti-cancer activity of anti-PD-1/PD-L1. Radiomics consists in the analysis of quantitative data extracted from standard medical imaging to generate imaging biomarkers. We developed a radiomics-based predictor of TIL and investigated whether such signature could predict the outcome of patients treated by anti-PD1/PD-L1.

Methods: We first developed a predictive model of tumor infiltrating CD8 T cells with RNA-Seq and raw imaging data (CT –Scan) using random forest in 69 HNSCC patients from the TCGA (The Cancer Genome Atlas)/TCIA (The Cancer Imaging Archive) database. CD8 T cells were estimated by the Microenvironment Cell Populations-counter signature. To validate our tool, this signature was applied to a first independent cohort of 100 patients for which the pathologic TIL was assumed as either high (lymphoma, melanoma, lung, bladder, renal and MSI+ cancers; 30 patients) or low (adenoid cystic carcinoma, low-grade neuroendocrine tumors, uterine leiomyoma; 70 patients). Finally, we applied our signature on a second cohort of 139 patients prospectively enrolled in anti-PD-1/PD-L1 phase 1 trials to infer its relation with patient outcome (Overall Survival).

Results: We developed a CD8 radiomics-based signature with six out of the 80 extracted features from CT-scans. As an internal validation, the correlation of this signature with the estimated TCGA CD8 was: spearman's rho=0.81 ($P < 1e-5$). In the first external cohort, this signature was associated with the assumed lymphocyteness (Wilcoxon test, $P < 0.001$). When validating our signature in the second external cohort, the median of the CD8 signature predicted score was used to separate patients into two groups. Patients with high predicted CD8 score had significantly better OS (HR = 0.55, 95%CI=0.36-0.86, P = 0.009) and the CD8 signature remained significant after multivariate analysis including RMH score and the number of previous lines of treatment (HR = 0.48, 95%CI=0.31-0.76, P = 0.002).

Conclusions: The radiomics-based signature of TIL was validated in two external cohorts. It appears a promising tool to estimate TIL and to infer the outcome of metastatic patients treated with anti-PD1/PD-L1.

Legal entity responsible for the study: Ferté Charles

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1633PD Co-amplification of KIT/KDR/PDGRA in over 100,000 advanced cancer cases

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Background: The 4q12 amplicon (4q12amp) which harbors the tyrosine kinases KIT, KDR and PDGFRA has been thought to occur as frequently as 3-7% in lung adenocarcinoma (LA) (Ramos et al, 2009) and 5-15% in glioblastoma (GBM) (Holtkamp, 2006; Szerlip, 2012) as assessed by a variety of techniques. As 4q12amp is hypothesized to be an oncogenic driver, it remains unclear whether all three kinases participate equally in oncogenesis, or if one kinase can be preferentially targeted by a tyrosine kinase inhibitor (TKI) for patient benefit. We undertook a large-scale genomic analysis to describe the frequency of 4q12 across solid tumors.

Methods: We prospectively analyzed 114,200 primarily advanced stage solid tumors in the course of clinical care using hybrid-capture based comprehensive genomic profiling (CGP) of 186 to 315 genes plus introns from 14 to 28 genes commonly rearranged in cancer.

Results: 4q12amp was present in 0.65% of all cases (740/114,200), with a median copy number of 10, and was most abundant in the following cancers: 4.8% of GBM (155/3,222), 0.83% of lung cancers (191/22,857, 2/3 approximately being LA), 1.9% of sarcomas (106/5,391), and 0.77% of breast cancers (92/11,980). Of sarcomas, 7.1% of osteosarcomas (26/367) and 2.82% of soft tissue sarcomas NOS (22/780) harbored 4q12amp. Of 4q12amp lung cancer cases, the supramajority (86%) did not harbor known oncogenic drivers of NSCLC (alterations of EGFR/HER2/MET, ALK/ROS/RET fusions, or BRAF V600E). Index cases of durable responses to pazopanib and imatinib will be described in undifferentiated sarcoma, synovial sarcoma, and head and neck/salivary cancers.

Conclusions: 4q12amp is significantly less frequent in GBM and lung cancer than previously reported by non-sequencing techniques, but is enriched in osteosarcoma and undifferentiated sarcomas. The driver status of 4q12amp is supported both by the predominant mutual exclusivity with other known drivers in lung cancer, and responses to various multi-TKIs. The specificities of the latter may help shed insight into whether singly or multiply targeting KIT/KDR/PDGFRA is a preferred approach for patient benefit.

Legal entity responsible for the study: Foundation Medicine

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Disclosure: U. Disel: Research agreement with Foundation Medicine, which provided funding to run a small number of genomic profiling assay (<15). R. Madison, J. Chung, A. Oztan, A. Benson, J. Webster, P.J. Stephens, A.B. Schrock, V.A. Miller: an employee of and has equity interest in Foundation Medicine Inc M. Gounder: No COI for this specific work. Advisory board or compensations: Tracon, Daiichi, Karyopharm, Epizyme, Amgen S.J. Klempner: Honoraria – Foundation Medicine, Inc. Consulting/Advisory Board – Lilly Oncology, Boston Biomedical S-H.I. Ou: Stock ownership Yes Membership of an advisory board or board of directors Genentech/Roche, Ariad, Pfizer, Novartis, Astra Zeneca Corporate sponsored research S. Ganesan: COI: Merck: Spouse is employee and owns equity Inspirata Inc.: am on SAB, own equity and have IP Novartis: consultant J.S. Ross: Employee of and has equity interest in Foundation Medicine Inc. paid speaker for several pharmaceutical companies. has equity interest in Sypher Inc. S. Ali: Employee of and have equity interest in Foundation Medicine. I own <5000 USD in stock in epizyme and exelexis. All other authors have declared no conflicts of interest.

1634P FGFR pathway genomic aberrations and response to FGFRs inhibitors

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Background: Fibroblast growth factor receptors (FGFRs) are broadly distributed transmembrane tyrosine kinase receptors. They promote cell development, differentiation, survival, migration, angiogenesis, and carcinogenesis. Specific FGFR aberrations was observed in certain cancers, some are known to be driver for tumor progression, and related to prognosis or sensitivity to cancer treatments. It is consistent to hypothesize that targeting these cancers with FGFR inhibitors would be therapeutically beneficial.

Methods: We lead a retrospective, descriptive, monocentric study, involving results of three phase I trials of Institut Gustave Roussy, for patients with refractory various solid tumors, previous selected on FGFR abnormality (amplification, single nucleotid variant (SNV), translocation). Primary endpoint was tumor response. Secondary endpoints were difference in tumor according to the type of mutation, and time to failure (TTF).

Results: 55 patients with median age of 55 years and various solid tumors were enrolled between February 16, 2011 and October 26, 2016. All patients had advanced or metastatic cancer with a median of 3.5 metastatic sites. They were heavily pretreated, in median 3 prior regimens of chemotherapy, 0 to 2 lines of targeted therapy, and one patient had immunotherapy. For patients with FGFR fusion proteins, 43% achieved partial response (PR). Median tumor response was - 46%, sustained response until 17 months. Response of SNV group depended on the type of mutation and degree of pathogenicity, in the different tumor locations. 20% had PR. Whereas some pathogenic mutations lead to dramatic response until 18 months; others failed to achieve tumor shrinkage or stabilization. 5% of patient with FGFR amplification had tumor response for 3 months only. Main clinical and biological toxicities were grade 1/2 and resolved after interruption. Treatment was resumed, at same or lower dose, excepted for 3 patients with permanently discontinuation. There was no death due to toxicity.

Conclusions: We identified genetic alterations in various members of the FGF/FGFR system that represent suitable predictive biomarkers to guide patient selection for treatment with selective pan FGFRs targeting agents.

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1635P FGFR 360° resistance: Establishing a translational research framework in FGFR-altered (FGFRalt) patients (pt) treated with fibroblast growth factor receptor inhibitors (FGFRinh)

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Background: Pt selection is critical for the future development of FGFRinh. Our institution aimed to implement a translational platform to obtain samples of FGFRalt pt included in phase 1 trials.

Methods: Prospective generation of a collection of pt samples with molecularly-selected FGFRalt tumors [amplified(amp)/mRNA high expression(mRNAh)/mutated(mut)/translocated(trans)]. We developed a protocol to obtain serial biopsies (bx) during therapy with an FGFRinh, including warm autopsies, for patient-derived xenografts (PDXs) generation. We collected plasma for analysis of circulating tumor DNA (ctDNA). Clinical benefit (ClinBen) was defined as any tumor shrinkage or disease control for 4 months.

Results: From 2014 to 2017, 40 FGFRalt pt were included [FGFRamp (20)/mRNAh (7)/mut(17)/trans (3)]. 30 cases received an FGFRinh [multi-tyrosin kinase (7), selective reversible-(8) or irreversible-FGFR1-4inh (14) or FGFR4inh (1)]. 8 cases achieved ClinBen (5 breast - 2 FGFR1amp, 2 FGFR1mut, 1 11q+FGFR2amp-/1 biliary tract FGFR2trans/1 head&neck FGFR1mRNAh/1 mullerian carcinosarcoma FGFR2mut). PDXs/bx after progression to FGFRinh (10) and warm autopsies of responding pt (2) will serve to study tumor heterogeneity and resistance mechanisms using novel high-throughput technologies. All PDXs (16 growing/14 in observation) will help in identifying potential predictive biomarkers and further characterizing the mechanism of action of FGFRinh *in vivo. In vitro* functional profiling of oncogenic activity of FGFRmut (17) will be performed. Blood samples will serve for developing in-house cfDNA analysis to monitor genomic evolution of these 40 pt.

Conclusions: We have succesfully developed a powerful precision medicine framework for linking the molecular biology with the best tumor models in parallel with early clinical research. By integrating the knowledge obtained from the analysis of relevant samples, we aim to validate future hypothesis-driven therapies for selected FGFRalt pt and guide the successful development of FGFRinh. Co-funded by *ISCIII-FEDER* (PI15/00360).

Legal entity responsible for the study: Vall d'Hebron Institute of Oncology

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1636P EPHA2 receptor is involved in in vivo acquired resistance to anti-Epidermal Growth Factor Receptor (EGFR) treatment in metastatic colorectal cancer (mCRC)

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Background: EPHA2 tyrosine kinase receptor is implicated in cell growth, migration, and invasiveness in a wide range of cancers. We studied its role as a potential marker of resistance to anti-EGFR drugs in colorectal cancer (CRC). We previously demonstrated that EPHA2 was differently activated among a panel of CRC cell lines with primary and acquired resistance to cetuximab and the use of ALW-II-41-27 (EPHA2 selective inhibitor) in combination with cetuximab was able to revert this resistance in *in vitro* experiments (abstract presented at 2016 ESMO Congress in Copenhagen). Here we present the study on *in vivo* models.

Methods: EGFR dependent SW48 and LIM1215 cell lines were engrafted into nude mice and treated with cetuximab until disease progression. Once tumors became resistant (SW48-CR and LIM1215-CR) mice were randomized in groups of 10 mice each and assigned to receive ALW- II-41-27 as single agent or in combination with cetuximab, no treatment and cetuximab alone group served as control. ALW- II-41-27 was administered daily at 30 mg/kg by oral gavage and cetuximab intraperitoneally at 1 mg/kg two days a week. Treatment was performed for three weeks, then mice were euthanized and protein expression in tumors was analysed by Western Blot.

Results: The combination of the two drugs induced a significant reduction of tumor volume since the first administration. A reduction of 50% of tumor volume was found in 5 out 10 LIM1215-CR mice treated with ALW-II-41-27 as single agent. This effect was maintained after cessation of therapy and induced prolonged survival. Tumor protein analysis by WB demonstrated a strong reduction of EPHA2 expression and activation in mice treated with the combination of ALW-II-41-27 and cetuximab, accompanied by a significantly inhibition of activated pMAPK and pAKT.

Conclusions: These results highlight the role of EPHA2 as a potential therapeutic target in mCRC treatment.

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

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Disclosure: All authors have declared no conflicts of interest.

1637P Eph A2 expression is a predictive biomarker of poorer activity and efficacy of FOLFIRI + cetuximab in RAS WT metastatic colorectal cancer (mCRC) patients (pts) in the CAPRI GOIM trial

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Background: Eph A2 promotes tumor growth, invasiveness and angiogenesis in mCRC. Targeting Eph A2 could overcome resistance to anti-epidermal growth factor receptor treatment in colon cancer preclinical models.

Methods: Formalin-fixed paraffin-embedded tumor specimens from 82 RAS wild type (WT) mCRC pts treated with cetuximab + FOLFIRI as first line therapy in the CAPRI GOIM trial were assessed for Eph A2 expression by immunohistochemistry. Eph A2 levels were evaluated developing an HSCORE [1 × (% cells 1+) + 2 × (% cells 2+) + 3 × (% cells 3+)] (range: 0-300). A cut off was set by ROC analysis to define high (>50) and low (≤50) Eph A2 levels.

Results: Eph A2 expression was found in 55/82 (67%) cases. According to HSCORE Eph A2 levels were low in 54 (66%) and high in 28 (34%) samples. Eph A2 expression resulted in mostly complete membranous staining. Tumor stroma was positive in 15/82 (18%) cases. In most of these cases an intense immune infiltrate was observed. Non-tumor adjacent normal mucosa was assessable in 34/82 samples. Eph A2 was expressed in 16/34 (47%), more frequently in dysplastic epithelial areas. A significant correlation between Eph A2 expression in tumor and stroma was found ($p < 0.0001$). Eph A2 was more frequently expressed in less differentiated tumors ($p = 0.02$), as well as in left-sided tumors compared to right-sided tumors [17/28 (61%), 11/28 (39%), respectively $p = 0.04$]. Eph A2 expression was associated with higher rate of disease progression (PD) 8/28 (29%) vs 5/54 (9%) ($p = 0.02$), and with worse median PFS [8.6 m (CI95% 6.4-10.8) vs 12.3 m (CI95% 10.4-14.2) $p = 0.030$], both in left and right-sided tumours. Moreover, median OS was 28.4 m (CI95% 13.1-43.7) vs 39.8 m (CI95% 30.2-49.4), although this result did not reach statistical significance ($p = 0.23$).

Conclusions: Eph A2 levels were significantly associated with a worse PFS and an increase in PD in RAS WT mCRC pts treated with cetuximab + FOLFIRI as first line therapy in the CAPRI GOIM trial, in both right- and left-sided tumors. A similar trend was observed for OS. Eph A2 might represent an additional predictive biomarker of lack of efficacy in RAS WT mCRC pts treated with cetuximab + FOLFIRI.

Legal entity responsible for the study: Department of Clinical and Experimental Medicine 'F. Magrassi' Università degli studi della Campania "Luigi Vanvitelli", Naples, Italy.

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Disclosure: F. Ciardiello: Advisory boards: Merck Serono, Lilly, Roche, Bayer, Amgen, Pfizer. E. Martinelli: Advisory boards: Merck Serono, Amgen. All other authors have declared no conflicts of interest.

1638P Clinical value of cfDNA and CTCs in EGFR mutations detected in advanced NSCLC

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Background: Targeted inhibition of EGFR represents a milestone in lung cancer treatment. Development of sensitive and accurate techniques allows the detection of EGFR mutations in liquid biopsies. CTCs and ctDNA analysis may be useful in treatment selection, response monitoring, and early resistance detection. The aim of this study was to correlate the EGFR mutational status of CTCs and cfDNA at diagnosis and during follow-up in non-small-cell lung cancer (NSCLC) patients.

Methods: The study included 22 EGFR mutated NSCLC patients, blood samples were collected and repeated sampling was performed during follow-up and at progression. cfDNA was obtained from plasma; whereas CTCs were isolated by size using a filtration-based device (ScreenCell), characterized and enumerated by H&E. CTC and cfDNA genotyping was performed by PNA-Taqman assay for EGFR 19del, L858R, G719X and T790M detection.

Results: Patient's median age was 65 years, 81.8% were female, 70% never-smokers and 94% were ADC. The follow-up ranged from 3 to 48 months. Out of the 22 *EGFR* mutated tumors identified, 12 harbored exon 19 deletion, 7 L858R mutation in exon 21, 2 G719X mutation and one presented exon 19 deletion and T790M together at diagnosed. All patients were treated with EGFR-TKIs. 110 blood samples were evaluated at baseline and during follow-up. CTCs were observed by H&E with a range 1-30/3 ml. Our results confirm that detected mutations can provide early outcome information. Early undetectable blood mutations after EGFR-TKI might predict a large clinical response, whereas in TKI-responders patients, *EGFR* mutation remained undetectable, its reappearance preceded disease progression. In case of persisted mutation during treatment, a rapid progression and exitus was observed. A baseline T790M mutation in EGFR TKI-naïve patient has been reported with rapidly progression and exitus.

Conclusions: Results suggest that analyses of EGFR mutations in CTC and cfDNA have important clinical implications and can be a useful biomarker of diagnoses, response to therapy and early detection of mechanisms of TKIs resistance, in advance of clinically detection. This work was supported by Astra Zeneca (ISSRES0110), the *RD12/0036/0025* ISCIII, grants from the FEDER and López-Trigo Grant.

Legal entity responsible for the study: Fundación para la Investigación del Hospital General Universitario de Valencia

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Disclosure: All authors have declared no conflicts of interest.

1639P Tucatinib, a HER2 selective kinase inhibitor, is active in patient derived xenograft (PDX) models of HER2-amplified colorectal, esophageal and gastric cancers

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Background: Tucatinib, an orally bioavailable and HER2 selective small molecule tyrosine kinase inhibitor, is currently being developed for HER2+ metastatic breast cancer in combination with capecitabine + trastuzumab (HER2CLIMB study). In addition to breast cancer, HER2 is amplified in subsets of patients with other malignancies, including gastrointestinal cancers (colorectal, esophageal and gastric cancers). To test whether tucatinib might have utility in treating HER2-amplified cancers originating from the gastrointestinal tract, tucatinib was tested alone, and in combination with trastuzumab, in cell line derived and PDX models of colorectal, esophageal and gastric cancer.

Methods: *In vitro* assays were performed to evaluate the combination of tucatinib and trastuzumab in HER2-amplified cell lines by measuring changes in signal transduction (pHER2, pHER3, pAKT) and cell survival. The *in vivo* activity of tucatinib (50 mg/kg BID) and trastuzumab (20 mg/kg Q3D) was evaluated alone, or in combination, in established HER2-amplified tumor models, including PDX models of colorectal, esophageal and gastric cancers.

Results: As a single agent, or in combination with trastuzumab, tucatinib demonstrated significant anti-tumor activity, including tumor regressions, in the N87 gastric cancer cell line xenograft model and in PDX models of HER2 amplified colorectal, esophageal and gastric cancers. The combination of tucatinib and trastuzumab was consistently more active than either single agent alone, and resulted in tumor growth inhibition from 85-139%, including complete tumor regressions in HER2+ gastric PDX models.

Conclusions: The activity of tucatinib in HER2-amplified colorectal, esophageal and gastric tumor xenograft models supports the exploration of using tucatinib to treat HER2+ gastrointestinal cancers in the clinical setting. To this end, an open label phase II clinical study combining tucatinib with trastuzumab in HER2+/RAS wild type metastatic colorectal cancer (MOUNTAINEER) has recently been initiated.

Legal entity responsible for the study: Cascadian Therapeutics

Funding: Cascadian Therapeutics

Disclosure: S. Peterson: Employee and shareholder of Cascadian Therapeutics, corporate officer of Cascadian Therapeutics. P. de Vries, J. Piasecki, R. Rosler: Employee and shareholder of Cascadian Therapeutics

1640P PI3K/RICTOR-mTORC2 axis as a driver of prognosis and potential druggable target in squamous cell lung carcinoma (SqCLC)

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Background: We built a risk classification model for resected SqCLC (R-SqCLC) by combining clinicopathological predictors to discriminate patients' (pts) prognosis (*Pilotto JTO 2015*), we externally validated this model in a pts' cohort of > 1,300 R-SqCLC (*Bria WCLC 2016*) and we performed an integrated multi-platforms genome analysis of prognostic outliers to identify potentially druggable modulators as the PI3K/RICTOR-mTORC2 axis (*Pilotto WCLC 2016*). Here, we validate our molecular findings and we enhance our rationale with *in vitro* studies.

Methods: Next Generation Sequencing (NGS) analysis of somatic mutations (SM) and copy number alterations (SCNA) was performed (Ion AmpliSeq Lung & Colon Cancer Panel: 22 genes, a SqCLC customized targeted NGS panel: 20 genes, the commercial Ion AmpliSeq Comprehensive Cancer Panel: 409 genes). In vitro experiments were performed using the SqCLC cell line H-1703 (Rictor amplified-6 copies). PF-05212384 [PI3K/mTOR inhibitor (inh)], AZD2014 (mTORC1/2 inh), MK-2206 (panAkt inh), everolimus (mTOR inh) and chemotherapeutic drugs (Docetaxel, Gemcitabine) were tested. Cell viability was assessed by crystal violet assay and the half maximal inhibitory concentration (IC50) was estimated to evaluate drug efficacy.

Results: Main results of overall 97 pts (Training/Validation: 60/37) are presented in the Table.

Table: 1640P

	Gene	Training Set [%]	Validation Set [%]
SM	TP53	53 [88.3]	27 [72.9]
	TIE1	4 [6.7]	2 [5.4]
	PTEN	6 [10]	4 [10.8]
	PIK3CA	3 [5]	3 [8.1]
SCNA Gains	RICTOR	13 [35.1]	14 [23.3]
	PIK3CA	17 [45.9]	26 [43.3]
	FRS2	8 [21.6]	7 [11.7]
	FGFR1	14 [37.8]	18 [30]
SCNA Losses	PTEN	5 [13.5]	19 [31.7]
	TSC2	8 [21.6]	7 [11.7]

The *in vitro* results support a significant inhibition of H-1703 cells proliferation by Gemcitabine, Docetaxel, PF-05212384, MK-2206 and AZD2014 with IC50 values of 0.4 nM, 0.45 nM, 10 nM, 66 nM, 110 nM, respectively. Everolimus was not effective.

Conclusions: Our multi-step genomic analysis performed in almost 100 R-SqCLC pts allowed us to identify altered pathways with a biological impact in SqCLC oncogenesis, as the *PI3K/RICTOR-mTORC2* axis. Moreover, our *in vitro* results justify pursuing mTOR inhibition, focusing on mTORC2 complex, in RICTOR-aberrant tumors.

Legal entity responsible for the study: Emilio Bria

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Disclosure: All authors have declared no conflicts of interest.

1641P Combination of duligotuzumab, anti HER3 antibody or taselisib, Pi3k inhibitor with trastuzumab shows synergistic antitumoral activity in HER2 positive gastric cancer cells (GCC)

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Background: The anti-HER2 monoclonal antibody Trastuzumab is central to the treatment of HER2-positive gastric cancer (GC); however, its responses are limited due to some poorly understood mechanisms of resistance. The aim of this study was to asses the antitumortal activity of Duligotuzumab, an anti HER3 antibody or Taselisib, a Pi3k inhibitor combined with Trastuzumab IN a panel of HER2 positive human gastric cancer cell lines (GCC), to improve anti HER2 treatment efficacy.

Methods: We evaluated in vitro the effect of Duligotuzumab, Taselisib and Trastuzumab in single agent and in combination treatments in HER2-positive GCG (NCI-N87, KATOIII, OE19) and in negative HER2 GCC (MKN28), through proliferation, migration and apoptosis assays. We also investigated the effect of combined treatment on downstream intracellular signaling, by western blot analysis.

Results: After establishing, through a dose response curve, the IC50 for each drug used ($\approx 0.5\ \mu M$), a significant synergistic effect of Duligotuzumab, Taselisib and Trastuzumab treatments in HER2-positive GCG was observed by reduction of proliferation and migration in KATOIII, OE19 and N87 cell lines; the same effect was found analyzing the apoptotic rate. At cellular level, in particular in KATOIII and OE19 cell lines, the combined treatment with Duligotuzumab or Taselisib plusTrastuzumab completely inhibited the activation of proteins downstream of HER3, PI3K and MAPK pathways.

Conclusions: Targeting both HER2 and HER3 or HER2 and PI3K with the combination of anti-HE3 antibody or Pi3k inhibitor with Trastuzumab results in an improved treatment effects on HER2-positive GCG. These important findings can be utilized to facilitate the design of future clinical trials.

Legal entity responsible for the study: University of Campania Luigi Vanvitelli

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1642P The TLR9 agonist lefitolimod modulates tumor microenvironment and improves anti-tumor effect of checkpoint inhibitors in vivo

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Background: Preclinical and ongoing clinical studies support the use of TLR9 agonists for immunotherapeutic approaches. Lefitolimod (MGN1703) is a covalently-closed dumbbell-like immune surveillance reactivator with broad immunomodulatory effects on the innate and adaptive immune system. Lefitolimod is currently evaluated in a phase 3 trial in mCRC patients (IMPALA), a phase 2 trial in SCLC patients (IMPULSE) and in two phase 1/2 trials, (i) in solid tumors in combination with the checkpoint inhibitor ipilimumab and (ii) in HIV patients (TEACH).

Methods: In several murine tumor models lefitolimod reduced tumor growth. Since the mode-of-action of lefitolimod starts upstream of the initiation points of checkpoint inhibitors like anti-CTLA-4 or anti-PD-1/anti-PD-L1 combinatory approaches may result in an enhanced anti-tumor effect. Therefore, two syngeneic murine models – the colon carcinoma CT26 and the lymphoma A20 model – were used for evaluation of the anti-tumor effect of lefitolimod with checkpoint inhibitors. In the CT26 model the influence of lefitolimod on tumor microenvironment (TME) was analysed.

Results: Treatment with anti-PD-L1 (i.p.) had no effect on tumor growth in the CT26 model, whereas addition of lefitolimod (s.c.) to anti-PD-L1 led to a clear anti-tumor effect (tumor growth inhibition, TGI 48%). This combinatory effect was even more pronounced in the A20 model where treatment with anti-PD-1 (i.p.) alone had a moderate anti-tumor effect which was vastly increased by the combination (TGI – anti-PD-1: 46%, anti-PD-1/lefitolimod 99%). Moreover, in the CT26 model an anti-tumor response to lefitolimod (i.tu.) was associated with increased infiltration of CD3 T-cells –more specifically CD8 T-cells – into the tumor of a CT26 model.

Conclusions: We showed that the member of dSLIM family of TLR9 agonists, lefitolimod, can enhance the limited anti-tumor effects of checkpoint inhibitors in murine colon carcinoma and lymphoma tumor models in vivo. The anti-tumor effect of lefito-

limod is associated with TME modulation with increased T-cell infiltration. These data clearly support the combination of lefitolimod with checkpoint inhibitors in clinical trials.

Legal entity responsible for the study: Mologen AG

Funding: Mologen AG

Disclosure: K. Kapp, B. Volz, D. Oswald, M. Schmidt: Employee of Mologen AG. B. Wittig: Consults Mologen AG and also receives funding from Mologen AG.

1643P Circulating immune-profile as predictor of outcome in advanced NSCLC patients treated with nivolumab

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Background: Detection of predictive markers of anti-PD-1/PD-L1 antibodies activity is of pivotal interest in non-small cell lung cancer (NSCLC). This study aimed to identify a circulating immuno-profile as predictor of outcome in NSCLC patients treated with nivolumab.

Methods: A peripheral blood immuno-profile evaluation was performed at baseline (T0), after 2 (T1) and 4 cycles (T2) of bi-weekly nivolumab in advanced pre-treated NSCLC patients from two Italian Institutions. First tumor assessment was performed after 4 cycles and then every 2 months. FACS analysis of lymphocyte subpopulations [CD3, CD4, CD8, NK (CD56), Treg (FOXP3) and MDSC] was performed. Absolute and % changes of lymphocyte subsets together with their functional and proliferative activity were assessed. Quali-quantitative leucocyte composition at baseline and its variation during therapy were correlated with tumor response and survival.

Results: In the overall population of 54 treated patients, baseline Neutrophil-to-Lymphocyte ratio and NK count, lymphocyte count and CD4 variations during therapy showed a statistically significant prognostic role ($p < 0.001$; $p = 0.012$; $p < 0.001$; $p = 0.010$, respectively). Among 31 patients (squamous carcinoma, n = 17; adenocarcinoma, n = 14) in which all 3 time-points samples were available, 19 were *responders* (response and stable disease) and 12 *non-responders*. In *responders*, absolute numbers of total NK and NKCD56dim subset were higher at baseline and their increase between T0 and T1 was statistically significant ($p < 0.05$). *Responders* also displayed increased cytotoxic capability as shown by a higher baseline expression of CD3ζ, perforin and granzyme in NKCD56dim subset. No significant variation was documented in absolute number and functional activity of CD4+ and CD8+ lymphocytes. A higher percentage of CD8+PD-1+ cells at baseline was observed in *responders*, while *non-responders* showed a statistically significant increase in the absolute number of MDSC during therapy ($p < 0.05$).

Conclusions: The number and function of NKs and the frequency of PD-1 expression in CD8+ cells could represent predictive peripheral immuno-biomarkers for nivolumab treatment in advanced NSCLC.

Legal entity responsible for the study: University Hospital of Parma

Funding: AIRC

Disclosure: All authors have declared no conflicts of interest.

1644P Monitoring the effect of cytostatic treatment by immune activity

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Background: Early prediction of effect remains an unsolved problem in cytostatic treatment of malignant tumors. The aim of the present study was to analyze the potential relationship between immune activity as measured by the NK Vue® system and response in patients with different tumors and different cytostatic regimens.

Methods: The study included six different trials encompassing patients with breast, prostate, ovarian and colorectal cancer. All protocols are still recruiting and so far 108 patients have been included. The preliminary results are based on 54 patients with response data available from the first evaluation. Blood samples were collected at baseline and prior to each treatment cycle into NK Vue™ Promoca tubes and placed in an incubator at 37 °C within 15 minutes of sampling. Following 24 hours of stimulation the plasma in each tube was harvested and analyzed for the level of interferon-gamma, as a surrogate for immune activity, by enzyme-linked immunosorbent assay using the NK Vue® Gold Kit.

Results: Similar results were seen between immune response and tumor types receiving different treatments. Consequently, data were pooled for preliminary evaluation. The outcome suggested a classification into three groups. The interferon-gamma dropped to an abnormal level (<200 pg/ml) in group 1 (27 patients) or remained at an abnormal level during treatment. In group 2 (12 patients) the level remained within a normal range (>500 pg/ml), while in group 3 (15 patients) it was raised from an abnormal to a normal level. The response rates were 11%, 42%, and 80% in the three groups, respectively. The difference was highly significant ($p < 0.001$). Accordingly, the positive and negative predictive values of a raising level were 80% and 79%.

Conclusions: The results suggest a relationship between the ability to mount an immune response upon stimulation and treatment effect comparable among different tumor types and treatments. Increasing levels of interferon-gamma shortly after initiation of treatment seems to predict treatment effect. Updated results will be presented at the meeting.

Legal entity responsible for the study: Vejle Hospital, Department of Oncology

Funding: ATGen

Disclosure: All authors have declared no conflicts of interest.

1645P Analysis of programmed death-ligand 1 (PD-L1) expression, transforming growth factor (TGF)-β gene expression signatures (GES) and tumor-infiltrating immune cells (IC) in hepatocellular carcinoma (HCC): Rationale for targeting PD-L1- and TGF-β

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Background: HCC evades antitumor immune responses via multiple mechanisms, including the PD-L1 and TGF-β pathways. PD-L1 expression correlates with tumor aggressiveness and recurrence. Increased TGF-β activity corresponds with poor clinical outcomes. Using immunohistochemistry (IHC), we previously showed that PD-L1 expression in HCC stems primarily from IC. To further assess the HCC immune milieu, we measured IC, TGF-β-associated GES, and PD-L1 expression using IHC/RNAseq.

Methods: We assessed protein expression in 50 resected HCC specimens by quantitative (Q) IHC (primary antibodies: PD-L1, CD8, CD68) using standard techniques and automated software. For RNAseq, we prepared strand-specific libraries from extracted RNA, which were sequenced and compared to GES from published papers, CIBERSORT and Ingenuity Pathway Analysis.

Results: All cases had typical morphology (low- to high-grade trabecular, pseudoglandular, or solid with common cytoplasmic features). Q CD8 IHC significantly correlated with CD8 mRNA expression and CD8 T cell GES, supporting the utility of RNAseq to evaluate the role of $CD8^+$ T cells in HCC. RNAseq identified TGF-β1 as the main TGF-β isoform in HCC. Predefined TGF-β GES correlated strongly with EMT GES. There was a trend toward increased TGF-β1 activity and EMT marker expression in the S1 molecular subtype, which has previously been associated with TGF-β-driven aberrant Wnt signaling. Q CD8 IHC correlated with PD-L1 mRNA and protein levels in IC. In samples with high CD8, there was a trend of increased tumor-associated macrophages (TAMs); the presence of TAMs strongly correlated with TGF-β GES. Interestingly, few tumor cells displayed membranous PD-L1 staining as confirmed by PD-L1/pan-cytokeratin double labeling.

Conclusions: We used RNAseq and IHC to better understand the immunosuppressive environment in HCC driven by TGF-β and PD-L1, which may mediate different mechanisms to inhibit preexisting $CD8^+$ IC.

Clinical trial identification: N/A

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1646P Clinical factors associated with mutation burden in non-small cell lung cancer

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Background: Mutation burden (MB) analysis is scarce in routine clinical practice. We aimed to identify predictive factors for amount of MB in patients with resected non-small cell lung cancer (NSCLC).

Table: 1646P Genetic alterations according to histologic subtype (N = 150).

ADC	n = 59 (100%)	SCC	n = 62 (100%)	SaC	n = 19 (100%)
KRAS		MET amp		METex14	
mut (exons 2-3)	14 (20%)	GA	3 (5%)	Mut	1 (5%)
wt	45 (80%)	NC	53 (85%)	wt	16 (94%)
		Unknown	6 (10%)	Unknown	2 (1)
EGFR		METex14		KRAS	
mut (exon18-21)	6 (10)	Mut	0	Mutation	4 (21)
wt	49 (83)	wt	58 (94)	wt	12 (63)
Unknown	4 (7)	Unknown	4 (6)	Unknown	3 (16)
ALK		PIK3CA amp		STK11	
Transloc.	1 (2)	GA	6 (10)	Mutation	1 (5)
wt	57(96)	NC	20 (32)	wt	15 (79)
Unknown	1 (2)	Unknown	36 (58)	Unknown	3 (16)
STK11		FGFR1 amp			
mut	10 (17)	Amp	9 (15)		
wt	46 (78)	NA	51 (82)		
Unknown	3 (5)	Unknown	2 (3)		
METex14					
Mut	2 (3)				
wt	50 (95)				
Unknown	7 (12)				
MET amp					
GA	4 (7)				
wt	51 (86)				
Unknown	4 (7)				
Co-mutation KRAS+STK11					
Mut	4 (7)				
wt	55 (93)				
Co-mutation KRAS+P53					
Mut	4 (7)				
wt	54 (91)				
Unknown	1 (2)				

Methods: We assessed somatic MB in surgical tumor specimens with whole exome sequencing (WES) using an ion torrent proton platform (Thermo Fisher Scientific). Two hundred forty-six NSCLC patients were randomly divided into training (n = 123) and validation (n = 123) cohorts. We defined patients with a greater than median number of non-synonymous (n-syn) mutations as the higher MB group. To detect higher n-syn MB in the training cohort, clinical data was assessed using a stepwise regression model. The validation cohort was subsequently analyzed. Also, the detected factors were validated via 100 repetitions of this procedure with different randomly divided cohorts using bootstrapping method.

Results: Out of 250 NSCLC patients with tumors surgically resected between September 2014 and September 2015, we analyzed tumors from 246 patients. Patient background: median age (range) 70 (39-87), male 63%, smoker 71%, pathological stage (p-stage) (I/II/III) 67/21/12% respectively, histological type (Ad/Sq) 78/22%, EGFR mutation (positive/wild type) 31/69%, median serum CEA level (range) 3.3 ng/ml (0.5-491.8), median serum CYFRA 21-1 level (range) 1.2ng/ml (1-38), median exonic MB (range) 62.5 (4-2144) [1.79 mt/Mb (0.1-61.4)], and median n-syn MB (range) 41 (1-1510) [1.17 mt/Mb (0.02-43.2)]. Stepwise regression analysis identified four factors [histological type: squamous, smoking status: smoker, age: greater than or equal to 70, and elevated serum CEA level (greater than 5ng/ml)] associated with high n-syn MB (p=.069, p=.0001, p=.106 and p=.037 respectively). In the receiver operating characteristic curves predicting high MB, the area under the curve for the four variables in the training and validation cohorts was 0.82 and 0.84, respectively. Squamous histology, smoker, and elevated CEA level showed highly reproducible in repeated random simulations (p = 0.93, 1.0, and 0.72).

Conclusions: Along with squamous histology and smoking, elevated CEA level may be an independent predictive factor for higher MB in NSCLC.

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1646P Integrative analysis of NSCLC identifies tumor genetic profiles associated with PD-L1 expression

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Background: PD-L1 expression is associated with clinical benefit from anti-PD1/anti-PD-L1 therapies in advanced NSCLC. However, additional biomarkers are needed to predict which patients will benefit most. The aim of this study is to correlate specific genomic alterations with immunological biomarkers in a cohort of NSCLC.

Methods: Patients diagnosed with NSCLC from 2000 to 2005 were retrospectively reviewed. Genetic mutations and copy number of selected genes were determined by Sanger and FISH. Immunophenotype was defined by PD-L1, HLA-1 and TILs CD8+ immunostaining and scored as follows: PD-L1 positivity $\geq$ 5% on membrane tumor cells; HLA-1 intensity: 0+,1+,2+; TILs CD8+ score: low or high infiltration. Statistical analysis using Chi-square test and logistic regression were performed.

Results: From 150 patients: 87% males; stage: 90% I-II, 10% III-IV; histology: 42% adenocarcinoma (ADC), 44% squamous (SCC), 14% sarcomatoid carcinoma (SaC). Genomic alterations according to histologic subtype are summarized in **Table**. PD-L1 was positive in 47% of tumors (49% of ADC, 43% of SCC, 58% of SaC), and correlated with TILs CD8 + (p <.001) and HLA-1 (p=.002). PD-L1 positivity was associated with *MET* alterations (4.5% MET amp, 2% METexon14 skipping), OR = 5.4 (1.4-21.2), p=.015. ADC harbouring *STK11* loss of function were correlated with negative PD-L1 (p = .01) and associated with immunosupressive phenotype (negative PD-L1, low CD8+), OR = 11.6 (2.1-64), p=.005. Distinct PD-L1 expression was evidenced in

KRAS mutant tumors according to additional co-mutations: 25% of *KRAS*+*STK11* were PD-L1+ whereas 75% of *KRAS*+*TP53* were PD-L1+, despite no statistically significance.

Conclusions: *MET* and *STK11* alterations were correlated with differential expression of tumor PD-L1. *STK11* mutant tumors were more likely to have an immunosupressive phenotype. Tumors harbouring specific genomic alterations might be enriched for distinct immunophenotypes which might contribute to rational use of immunotherapies.

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1648P B7-H3 (CD276) on circulating epithelial tumor cells (CETCs) correlates with proliferation marker Ki-67 and may be associated with aggressiveness of tumor in breast cancer patients

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Background: CETCs in the peripheral blood are a prerequisite for the development of metastases. B7-H3 is an important immune checkpoint member of the B7 family and inhibits T-cell mediated anti-tumor immunity. It is highly overexpressed on a wide range of solid cancers and often correlates with both negative prognosis and poor clinical outcome in patients. Based on the clinical success of the inhibitory immune checkpoint blockade, mAbs against B7-H3 appear to be promising therapeutic strategy. In order to better understand the role of B7-H3 in cancer development we used a non-invasive, real-time biopsy for determining B7-H3 on CETCs in breast cancer patients.

Methods: Blood from 50 patients suffering from breast cancer were analyzed for CETCs. The number of vital CETCs and the expression of B7-H3 and Ki-67 were evaluated using the maintrac® method.

Results: CETCs were detected in all examined patients (ranged from 2-676 CETCs in 100 µl of blood). B7-H3 expression on the surface of CETCs was found in 82% of patients. Triple negative breast cancer patients had statistically significantly more B7-H3 positive CETCs than patients with hormone receptor positive tumor tissue (median 50 vs. 26.3; $p < 0.05$). The frequency of B7-H3 positive CETCs was significantly higher in patients who received radiation therapy compared to patients without irradiation (mean 42 vs. 29; $p < 0.05$). B7-H3 positive CETCs seem to be more aggressive because the percentage of B7-H3 positive CETCs correlated with the percentage of proliferation marker Ki-67 positive CETCs ($r = 0.689$ and $p < 0.001$). Interestingly, a significant relationship between Ki-67 expression level on the CETCs and nodal status was found.

Conclusions: Breast cancer patients have detectable CETCs with high frequency of B7-H3 expression regardless of stage of disease. B7-H3 seems to be an important factor in immune evasion and may be a promising target of anticancer therapies. Furthermore, radiation leads to an up-regulation of B7-H3 expression on CETCs, which could be a possible mechanism of acquired radio-resistance.

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1649P Survival of non-small cell lung cancer patients predicted from expression of PD-L1, HLA class I and MICA/B on tumor cells

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Background: Several groups have reported that programmed death-1 (PD-1) ligand 1 (PD-L1) overexpression on tumor cells predicts a poor prognosis in patients with non-small cell lung cancer (NSCLC). Although recent studies have shown that PD-L1 overexpression on tumor cells predicts for improved clinical outcome in NSCLC patients treated with anti-PD-1/PD-L1 immunotherapy, PD-L1 low/negative tumors also benefit from anti-PD-1/PD-L1 immunotherapy. These findings suggest that study on multiple immune parameters should be considered. We recently reported that the overexpression of PD-L1 in tumor predicted a poor prognosis while overexpression of NK cell activating ligand MICA/B predicted improved clinical outcome in patients with resected NSCLC. It is well known that both T cell- and NK cell-mediated tumor recognitions are influenced by HLA class I molecules, however, the roles of HLA class I molecules are different between T cells and NK cells; HLA class I/T cell receptor immune synapse induces antigen-specific cytotoxicity by T cell, while HLA class I/killer cell immunoglobulin-like receptor synapse attenuates NK cell-mediated cytotoxicity. Here, we assessed the multiple immune parameters (PD-L1, MICA/B, and HLA class I) in NSCLC tissues to assess the prognostic factors in patients with resected NSCLC.

Methods: We examined resected tumor tissues from 91 patients with pathological stage IA-IIIA NSCLC using immunohistochemical reaction for the expression of PD-L1, MICA/B, and HLA class I then assessed whether the multiple immune parameters impact on the clinical outcome of patients with NSCLC.

Results: PD-L1^{low}/MICA/B^{high} tumors have an excellent disease free survival time (DFS) compared with PD-L1^{low}/MICA/B^{low} (p=0.010 by log-rank test) or PD-L1^{high} (p<0.01) tumors. Additionally, MICA/B^{high}/HLA class I^{high} tumors have improved DFS compared with MICA/B^{low}/HLA class I^{high} tumors (p=0.035).

Conclusions: Multiple immune parameters using the expression status of MICA/B and PD-L1 or HLA class I on tumor cells are useful prognostic factors for NSCLC. We should have more concerns to NK cell-mediated tumor elimination in anti-PD-1/PD-L1 immunotherapy.

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1650P YKL-39 induces monocytes migration and angiogenesis and inversely correlates with metastasis in patients with breast cancer

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Background: Human chitinase-like proteins are considered as biomarkers of cancer and chronic inflammation.YKL-39 is a unique member of chitinase-like protein family due to its presence only in humans but not in rodents both on gene and protein levels. However, its biological activity and association with tumor progression remains unknown.

Methods: YKL-39 expression and secretion in human monocytes-derived macrophages was measured by RT-PCR and ELISA. Monocyte migration was analyzed in a transwell system. In vitro tube formation assay was performed using HUVEC cells.112 female patients with nonspecific invasive breast cancer of stage IIA-IIIC (T1-4N0-3M0) were included in the study. Confocal microscopy analysis was used to identify cell type expressing YKL-39 in tumor samples.YKL-39 expression level was measured by RT-PCR in tumor biopsy specimens.

Results: Human monocytes-derived macrophages differentiated in the presence of IL4 and TGFbeta, but not IL4 alone, were found to express high levels of YKL-39 mRNA and protein. Purified YKL-39 significantly enhanced the migration of human CD14+monocytes by 1.9 fold ($p < 0.01$) after 1 h, and 4.9 fold ($p < 0.01$) after 3 h that was comparable with the effect of MCP-1. In vitro tube formation assays using HUVEC cells demonstrated that YKL-39 has a strong pro-angiogenic effect. In human samples of breast cancer YKL-39 was found to be expressed in CD68+ macrophages but not in cancer cells or other stromal cell types. In breast cancer biopsy specimens it was found that high YKL-39 gene expression correlated with the significantly reduced frequency of lymphatic and hematogenous metastasis. Furthermore, high level of YKL-39 expression associated with 100% metastatic-free survival rate ($p = 0.015$).

Conclusions: TGFbeta is a key cytokine inducing production of YKL-39 in macrophages. YKL-39 stimulates critical for tumor progression processes: chemotaxis of monocytes and angiogenesis. However high levels of YKL-39 expression in tumor samples are predictive for metastatic-free survival in patients with breast cancer, suggesting that YKL-39 can program monocytes and newly growing vessels to inhibit metastatic spread.

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Disclosure: All authors have declared no conflicts of interest.

1651P Pre-treatment neutrophil lymphocyte ratio/platelet lymphocyte ratio as surrogate markers of survival in non-metastatic head and neck cancer patients: An observational study

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Background: Neutrophil lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) are known to be surrogate markers of inflammation and have been shown to predict mortality in patients with heart disease and cancer. In this study, we evaluate the

influence of pre-treatment NLR and PLR on overall survival in head and neck cancer patients.

Methods: In this observational correlational study, subjects with a diagnosis of non-metastatic head and neck cancer were analyzed for neutrophil-lymphocyte ratio and the platelet-lymphocyte ratio at baseline before the start of their cancer-directed therapy.

Results: In this study, 189 subjects were analyzed for neutrophil-lymphocyte ratio and platelet-lymphocyte ratio before their treatment. The mean age of the study sample was 54.5±11.8. Forty-two percent underwent surgery followed by adjuvant chemoradiation while remaining underwent concurrent chemoradiation. Neoadjuvant chemotherapy was done in 29.4% of the study population. Mean NLR was 3.4±3.13 and PLR was 12.7±8.8. ROC analysis revealed 2.23 as the cutoff for NLR and 9.49 as the cutoff for PLR. Based on these cutoffs a Kaplan-Meir analysis on overall survival showed significantly improved survival (67.5% vs 58% at their mean estimates of 52 and 36 months) in those with <2.23 NLR ratio compared to > 2.23 (Log Rank $\chi2$=5.3, p = 0.02). Similarly, those with <9.49 PLR had better overall survival (69% vs 56% at their mean estimates of 46 and 39 months) compared to > 9.49 (Log Rank $\chi2$=8.1, p = 0.005). Lower NLR also showed better disease-free survival (44 vs 33 months, Log Rank $\chi2$=4.8, p = 0.03) and lower PLR also showed better disease-free survival (44 vs 33 months, Log Rank $\chi2$=8.2, p = 0.004).

Conclusions: Both NLR and PLR are inflammatory biomarkers in cancer. The results from this study suggest pretreatment NLR and PLR as predictive markers of survival in non-metastatic head and neck cancer patients.

Legal entity responsible for the study: Vijay Agarwal

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1652P Enhanced antitumor activity of fixed-dose combinations of celecoxib and antihypertensives

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Background: Inflammation and hypertension have recently emerged as causal factors for tumor progression and anti-hypertensive agents have been shown to reduce inflammation and suppress tumor growth and metastasis. Cyclooxygenase-2 (COX-2) is upregulated in most human tumors and is a potent inducer of cancer-associated inflammation. This preclinical study evaluated a novel combination of a COX-2 inhibitor with three antihypertensive drugs to suppress tumor growth and metastasis.

Methods: Three anti-hypertensive drugs: i) Lisinopril [LIS], an inhibitor of Ang I converting enzyme (ACE); ii) Olmesartan medoxomil (OLM), an Ang II receptor blocker (ARB); and iii) Hydrochlorothiazide (HCTZ), a thiazide diuretic along with Celecoxib [CEL], a COX-2 inhibitor were evaluated either alone or in combination for tumor growth suppression and metastatic spread in an orthotopic inflammatory breast cancer (IBC)/SUM149 model and subcutaneous melanoma/MDA-MB-435, glioblastoma/U87, and IBC/SUM159 models. Luciferase-tagged SUM149 and MDA-MB-435 cell lines were used to determine the incidence and the burden of locoregional and systemic spread. Mice were monitored for weight loss, tumor volume and survival outcome. Metastasis was measured as luciferase expression in lymph nodes and lungs and normalized to total protein.

Results: In the orthotopic SUM149 model, OLM and CEL plus OLM, had a statistically significant decrease in tumor burden (2.4 ± 0.6 x10^4 RLU/mg of protein, p = 0.01 by Mann-Whitney test) in the ipsilateral lymph nodes versus the saline-treated control (17.6 ± 8.6 x10^4 RLU/mg of protein). Similar trend was observed for LIS, but not for HCTZ. In the subcutaneous model, synergistic antitumor activity was observed with OLM (p = 0.026) at low dose but not with LIS and CEL (p = ns). At high dose, LIS, OLM, and CEL showed significant inhibition of tumor growth but no synergy. HCTZ, an antihypertensive diuretic which has no direct impact on the vascular wall had no effect on tumor growth.

Conclusions: These preclinical data strongly suggest a hitherto unappreciated role of ACE/ARB in tumor growth control and support the further exploration of combinations of CEL with ACE/ARB in cancer, especially inflammatory breast cancer.

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Disclosure: All authors have declared no conflicts of interest.

1653P Overexpression of toll-like receptor 9 (TLR9) in elderly cancer patients when compared to cancer-free elderly control group

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Background: the genes of toll-like receptors (TLR) have been described as related to the immunosenescence process and carcinogenesis. The relationship of this gene family with carcinogenesis and immunoregulatory responses seems a promising field. The aim of this study is to compare the expression of TLR9 between geriatric cancer patients and elderly patients without any personal or familiar history of cancer, establishing if there are significant differences that may be explained by the carcinogenesis process rather than the immunosenescence one.

Methods: Between 2015 and 2016, a prospective cohort study including 195 elderly patients (≥ 60 years), 120 with incident cancer at the time of admission and 75 without any personal or familiar cancer history, assessed and collected sociodemographic and clinical variables and performed analysis of the peripheral blood in translational exploratory study. Determination of TLR9 was performed by flow cytometry with monoclonal antibodies anti-TLR9. Statistical analysis of the data was performed with GraphPad Prism.

Results: 120 patients with incident prostate or breast cancer and 75 patients without any personal or familiar history of cancer, both with ≥ 60 years, were included. Most of the cancer patients were male (60%), while most of the patients without any cancer history were female (75%). Comparing the percentage and fluorescence values of TLR9 expression, there are significant differences (p < 0,0001) between the cancer patients group and the one without any personal or familiar cancer history.

Conclusions: There is significant difference between the expression of TLR9 in elderly cancer patients and elderly patients without personal or familiar history of cancer.

Legal entity responsible for the study: Jurema Telles de Oliveira Lima

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Disclosure: All authors have declared no conflicts of interest.

1654P NSCLC patient immune cell profiling and response of tumor antigen specific CD8 T cells to checkpoint receptor antagonists

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Background: The breakthrough in cancer immunotherapy of targeting PD-1 or PD-L1 and enabling T cells to attack tumor has opened new window for cancer treatment of many tumor types. Many of these immunotherapeutic approaches involve targeting specific immune checkpoints. To better understand the role of checkpoint receptors in cancer immunotherapy and explore new treatments, we analyzed cancer patient PBMCs and dissociated tumor samples from non-small cell lung cancer (NSCLC).

Methods: Transcripts of Cancer Testis (CT) antigens (NY-ESO-1, MAGE-A1, and MAGE-A3), a novel T cell inhibitory checkpoint receptor (TIGIT), and its respective ligands (PVR and PVRL2) as well as PDL1 from a cohort of NSCLC patients was analyzed. Immune cells from these patient samples were profiled and NYESO1/HLAA2 tetramer was used to detect NYESO1 specific CD8 T cells in HLAA2+ patients. Intracellular cytokine secretion was analyzed using a specially designed multiparameter flow cytometry panel for both general and NYESO-1^+ CD8 T cells.

Results: The correlation between CT antigens, immune checkpoints, and effector T cell signature (CD8A, IFN-gamma, and Granzyme A) may help us understand 1) why certain patients have inflamed tumors and others have "cold" tumors; 2) why certain patients respond to anti-PD(L)1 therapy and others do not respond. Antibodies targeting both PD1 and another novel immune checkpoint receptor TIGIT showed best stimulatory effect on both antigen specific CD8 T cell number and intracellular IFN-gamma staining of those cells.

Conclusions: The data suggest that immune checkpoint receptor antibodies can be screened in real patient immune cells. Cotargeting multiple immune checkpoint receptors may provide superior efficacy to targeting single immune checkpoint receptor.

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Disclosure: All authors have declared no conflicts of interest.

1655P Effect of neoadjuvant chemotherapy on correlation of tumor-associated macrophages with angiogenesis and lymphangiogenesis in human breast cancer

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Background: Promoting role of tumor-associated macrophages (TAM) in angiogenesis and lymphangiogenesis was demonstrated in mouse tumor model sand human cancers. However, our latest studies revealed that amount of TAM in patients with breast cancer before as well after neoadjuvant chemotherapy (NAC) reversely correlated with

lymphatic metastasis. Our aim was to analyse the effect of NAC on correlation of TAM in intratumoral compartments with angiogenesis and lymphangiogenesis.

Methods: 115 female patients with breast cancer T1-4N0-3M0 were included in the study. 36 patients did not receive NAC, 79 received NAC. Expression levels of CD68 (general macrophage marker), stabilin-1 (marker of M2 macrophages), CD31 (marker of blood vessels) and LYVE1 (marker of lymphatic vessels) were identified by immunohistochemistry in 5 distinct areas of tumors: 1) soft fibrous stroma; 2) coarse fibrous stroma; 3) areas of maximum stromal-and-parenchyma lrelationship; 4) parenchymal elements; 5) gaps of ductal tumor structures.

Results: In breast cancer samples of patient who did not receive NAC direct correlation of CD68 expression in soft fibrous stroma and CD31 expression in coarse fibrous stroma ($r = 0,87$;$p=0,02$) was identified. However, reverse correlation was found between CD68 expression in gaps of ductal tumor structures and LYVE1 expression in soft fibrous stroma ($r=-0,89$;$p=0,04$). In contrast, in patients after NAC we identified a direct correlation between expression of CD68 and LYVE1 expression in the gaps of ductal tumor structures ($r = 0,80$;$p=0,02$). Expression of stabilin-1 in coarse fibrous stroma directly correlated with amount of LYVE1+ cells in areas with maximum stromal-and-parenchymal relationship ($r = 0,76$;$p=0,04$), but reversely correlated with the amount of CD31+ vessels in soft fibrous stroma ($r= - 0,52$;$p=0,001$).

Conclusions: Our data suggest that TAM before treatment support tumor angiogenesis however protect against lymphangiogenesis. After NAC TAM can switch their functional phenotype, do not support angiogenesis anymore but support lymphangiogenesis. The mechanism of chemotherapeutic programming of TAM remains to be identified.

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Disclosure: All authors have declared no conflicts of interest.

1656P Myeloid-derived suppressor cells are associated with a decrease of tumor antigen-specific Th1 immunity in non-small cell lung cancer

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Background: Myeloid Derived Suppressor cells (MDSC) are immune suppressive cells associated with poor survival in several cancers. In this study, we investigated their impact on spontaneous tumor antigen specific Th1 responses in Non-Small Cell Lung Cancer (NSCLC).

Methods: Monocytic MDSC (M-MDSC) ($Lin^{-}HL\text{-}DR^{-/lo}CD11b^{+}CD14^{+}CD33^{+}$) were measured in peripheral blood of 122 NSCLC patients and 34 healthy donors by flow cytometry. The presence of spontaneous anti-tumor Th1 response was measured by IFN-ɤ ELISPOT assay using mixture of peptides derived from lung cancer-associated tumor antigens such as telomerase, NY-ESO1 and Wilms Tumor-1. Patients' samples were collected at baseline before any treatment.

Results: Higher percentage of circulating M-MDSC was found in NSCLC patients compared to healthy subjects (mean: $3.9\pm0.4\%$ vs $1.5\pm0.4\%$, $p < 0.01$). Most patients presenting high level of M-MDSC in blood ($\geq$ 5%: $M\text{-}MDSC^{hi}$) belonged to metastatic stage (34%, 21/61) compared to 14%, 9/61 in localized disease ($p < 0.01$). However, $M\text{-}MDSC^{hi}$ status was associated with poor survival regardless the tumor stage (median OS: 11 vs 27 months in $M\text{-}MDSC^{hi}$ and $M\text{-}MDSC^{lo}$ groups respectively, $p < 0.001$). The IFN-ɤ+ antitumor specific T cell response was detected in 55.8% of patients and this frequency significantly dropped to 20% in $M\text{-}MDSC^{hi}$ group. Furthermore, the magnitude of this response changed according to M-MDSC level (231 vs 116 IFN-ɤ+ specific T cells in $M\text{-}MDSC^{lo}$ and $M\text{-}MDSC^{hi}$ respectively $p < 0.05$). Finally, patients having both $M\text{-}MDSC^{hi}$ status plus low anti-tumor T cell response exhibited a very poor survival (median OS of 6 months).

Conclusions: Our results show that high levels of circulating M-MDSC is associated with a decrease of pre-existing antitumor T cell response. The level of M-MDSC combined with antitumor T cell responses could predict distinct clinical outcome. Thus, monitoring M-MDSC in blood could be used as relevant immune biomarker in NSCLC.

Legal entity responsible for the study: Adotevi Olivier

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1657P Revealing potential immune responses (IRs) in patients with advanced colorectal cancer (aCRC) on first line chemotherapy: A prospective study of neutrophil to lymphocyte ratio, immune function and outcome

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Background: Neutrophil to lymphocyte ratio (NLR), a broad measure of inflammation and immune function, predicts outcome including overall survival (OS) in aCRC but the underlying mechanisms are unclear. Better understanding of IR in these patients may identify potential responders to novel immunotherapy. We investigated whether immune function correlated to NLR and how this altered during chemotherapy.

Methods: Peripheral blood was taken from 29 aCRC patients receiving 1st line chemotherapy (baseline and 6 weeks). NLR of ≥ 5 was defined as high. Immune function of peripheral blood mononuclear cells (PBMCs) was determined by NK cell activity (degranulation by CD107 expression and cytotoxic potential by ^{51}Chromium release) against target tumour cells, T cell activity by IFN-γ ELISpot, cytokine secretion (Luminex) and immune cell activation (flow cytometry).

Results: High baseline NLR was associated with shorter OS compared to low NLR (6.6 vs. 18.8 months; HR = 3.6 [1.25 to 10.35] $p = 0.0024$). High NLR also correlated with a depressed IR, including decreased cytolytic activity of PBMCs ($p = 0.046$), NK cell degranulation at baseline and decreased levels of certain immune stimulatory cytokines. Low baseline NLR correlated with increased T cell activity against tumour-associated carcinoembryonic antigen (CEA) after 6 weeks of chemotherapy. Higher cytotoxic activity of PBMCs against target tumour cells at baseline (seen in the majority of patients with NLR <5) was associated with increased OS ($p = 0.04$). A drop in NLR during chemotherapy was associated with increased innate immune function as determined by NK cell degranulation ($p = 0.004$). Irrespective of NLR, frequency of Tregs reduced during chemotherapy and there was an increase in PD-1 expression on CD8+ T cells ($p = 0.043$), NK cells ($p = 0.035$) and monocytes ($p = 0.016$).

Conclusions: This study supports the poor prognosis of a high baseline NLR in aCRC and demonstrates its association with an attenuated IR. Chemotherapy can partially reverse this phenomenon, potentially enhancing anti-tumour immunity. If chemotherapy leads to a more effective anti-tumour IR, sequential immunotherapy could exploit this.

Legal entity responsible for the study: University of Leeds

Funding: Cancer Research UK, Yorkshire Cancer Research

Disclosure: All authors have declared no conflicts of interest.

1658P Somatic loss of the wild-type BRCA1 allele is not necessarily the first event in the pathogenesis of hereditary ovarian cancer: Implications for novel mechanism of acquired platinum resistance

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Background: Ovarian cancers (OC) arising in BRCA1 germ-line mutation carriers usually demonstrate high sensitivity to neoadjuvant chemotherapy (NACT), but almost inevitably relapse even after complete cytoreduction and continuation of systemic platinum treatment after surgery.

Methods: Changes in the somatic BRCA1 loss-of-heterozygosity (LOH) status were monitored in OC samples obtained before NACT, after NACT and at disease relapses.

Results: Loss of the wild-type BRCA1 allele was documented in 19 out 28 chemonaive OC samples included in the study. Surprisingly, 13 (68%) of these 19 OC demonstrated the retention of BRCA1 heterozygosity in the tumor tissue, which was surgically removed after median 3 cycles of NACT. TP53 mutations were easily detectable in some of the post-NACT samples thus confirming the good quality of microdissection. FISH assay and the analysis of adjacent SNPs revealed that the reversion of LOH status was attributed to selection of preexisting BRCA1-proficient clones but not to the second mutation in BRCA1 gene. Four tumor relapses were available for analysis; 3 out of these 4 tumors "restored" BRCA1 LOH during platinum-free interval. Next-generation sequencing analysis identified additional molecular events associated with evolution of OC clones upon platinum exposure and during treatment-free periods.

Conclusions: Isolated BRCA1 proficient cells are still present in chemonaive ovarian carcinomas with BRCA1 LOH, indicating that the somatic loss of the wild-type BRCA1 is not necessarily the first event in the pathogenesis of hereditary OC. These clones rapidly expand during even short-term systemic therapy. BRCA1-deficient cells have selective advantage in the absence of drug exposure and repopulate the tumor mass during platinum-free intervals. These fluctuations of BRCA1 LOH status explain why conventional platinum-based therapy, being capable to produce excellent tumor responses in BRCA1 germ-line mutation carriers, is not curative when considering long-term outcomes.

Legal entity responsible for the study: Laboratory of Molecular Oncology, N.N. Petrov Institute of Oncology, St.-Petersburg

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Disclosure: All authors have declared no conflicts of interest.

1659P Role of UBR5 mutations in DNA damage response in mantle cell lymphoma

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Background: Mantle cell lymphoma (MCL) accounts for 7% of non-Hodgkin lymphomas and represents a particularly challenging disease with patient outcomes inferior to most other lymphoma subtypes. We recently reported frequent mutations (18%) in *UBR5*, a gene encoding an E3 ubiquitin-protein ligase that has not been previously implicated in lymphomagenesis. All mutations were clustered within 100bp in or around exon 58 of UBR5 and are predicted to result in the loss of the conserved cysteine residue, which is responsible for binding the ubiquitin molecule. The recurrence and clustering of *UBR5* mutations suggest their critical pathogenic nature in MCL that might be therapeutically targetable. The aim of this study is to determine the specific role of *UBR5* mutations in the pathogenesis of MCL.

Methods: Mutations clustering in exon 58 of *UBR5, a*s seen in MCL patients, were generated in three MCL cell lines (Granta-519, Jeko-1, and Mino) using the CRISPR-Cas9 genome engineering tool. First, global proteomes of *UBR5* mutants and WT were analyzed by Tandem Mass Tag (TMT)-based mass spectrometry to identify proteins with differential expression due to the *UBR5* mutations. Next, mass spectrometry-based immunoprecipitation proteomics (IP-MS) was employed to identify *UBR5* interacting partners. Candidate *UBR5* interacting proteins were functionally validated by flow cytometry, western blotting, co-immunoprecipitation, and immunofluorescence.

Results: The global proteome and IP-MS analyses identified a number of DNA damage response, chromosome organization, and cell cycle response proteins as the predominant proteins affected ($p < 0.05$). Our functional validation experiments show differential G2/M checkpoint activation and aberrant DNA damage response in *UBR5* mutants *vs* WT through association of UBR5 with ATM interactor ATMIN.

Conclusions: The proteome and functional analyses are consistent with *UBR5* functioning as a key regulator of cell signalling and point to the critical role of *UBR5* as a novel regulator of DNA damage response. Next, our goal is to develop mouse xeno-transplantation MCL models and identify therapeutic agents that render sensitivity in xeno-transplantation models with UBR5 mutations.

Legal entity responsible for the study: Centre for Lymphoid Cancer, Vancouver, British Columbia, Canada

Funding: The Terry Fox Foundation

Disclosure: All authors have declared no conflicts of interest.

1660P ATM role in prostate cancer (PrCa) progression and survival

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Background: Germline and/or somatic aberrations in *ATM* gene have been recently identified in up to 5% of PrCa cases. It has been also described that mutations in DNA repair genes predispose individuals to more aggressive and lethal phenotypes. For these reasons, our goal is to investigate the role of *ATM* in PrCa progression.

Methods: To study the cooperation of *Atm* in prostate cancer progression *in vivo*, we crossed the transgenic mouse model TRAMP with *Atm* null mice in C57BL/6 background. This model allows us to elucidate the progression of prostate cancer in wild-type (+/+), heterozygous (+/-), and homozygous (-/-) *Atm* loss in mice. PIN, invasive and metastatic prostate cancer as well as survival curves were compared for the three arms. In addition, in a large cohort of mCRPC (n = 419) from the prospective PROREPAIR-B study (NCT03075735), in which a large panel of germline DNA repair genes were studied, we compared the clinico-pathological characteristics at baseline and mCRPC diagnosis between germline *ATM* mutation carriers and non-*ATM* carriers. Chi-Square and Exact Fisher test, the Kaplan-Meier method and Long-rank test were used for statistical analyses.

Results: Twenty eight $TRAMP^{(T/+)}$; $Atm^{(+/+)}$ and 45 $TRAMP^{(T/+)}$; $Atm^{(+/-)}$ mice were follow-up until sacrifice-endpoint. Heterozygous *Atm* loss mice presented higher frequency of metastasis in the necropsy compared to *Atm* wild-type (44% vs. 21%, $p = 0{,}045$) and shorter median survival (26 vs. 32 weeks, $p = 0{,}008$). There were not significant different observed in PIN or invasive tumour prevalence. $TRAMP^{(T/+)}$; $Atm^{(-/-)}$ mice were excluded from analyses due to the early development of lethal thymomas requiring sacrifice before week 16. On the other hand, 8 patients out of 419 were found to harbour germline pathogenic *ATM* mutations (1.9%), and compared with non-*ATM* carriers presented higher frequency stage IV at diagnosis (63% vs. 34%, $p = 0.2$), bone metastasis (100% vs. 82%, $p = 0.4$) without other relevant differences found in these preliminary analyses.

Conclusions: Aberration in the *ATM* gene may favour metastatic progression in PrCa in prostate cancer preclinical models, although its clinical implication will require further clarification in the future.

Clinical trial identification: Part of the results came from the prospective PROREPAIR-B study (NCT03075735)

Legal entity responsible for the study: Spanish National Cancer Research Centre

Funding: Prostate Cancer Unit-Spanish National Cancer Research Centre

Disclosure: All authors have declared no conflicts of interest.

1661P Synergistic inhibition of CEP55 induces mitotic catastrophe and specifically targets aggressive breast cancer

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Background: Triple negative breast cancers (TNBCs) are the most aggressive and profoundly heterogeneous form of breast cancer (BC), treatment of which is a prevalent challenge faced in clinics. *CEP55*, discovered first by our laboratory, is a key regulator of cytokinesis, error in which roots to multi-nucleation. Function of CEP55 is critically delimited by ERK2/PLK1 dependent phosphorylation, for accurate cytokinesis. Research has demonstrated connotation of CEP55 with numerous cancers including BC as higher CEP55 mRNA expression is allied to worse prognosis and poor survival. We hypothesised that, CEP55 controls fate of aneuploid cell population among aggressive BC that are heavily reliant on mitotic genes for tumour progression, thus can be targeted for therapy development.

Methods: Using *in vitro* studies we demonstrated that depletion of CEP55 sensitizes TNBC cells to anti-mitotic drugs like PLK1 inhibitor to induce CDK1-Caspase 3-dependent mitotic catastrophe due to unscheduled CDK1/Cyclin B activation. Also we showed ERK1/2 transcriptionally controls CEP55 hence inhibition of MEK1/2 using the small molecule inhibitor Selumetinib, can mimic depletion of CEP55 *in vivo*.

Results: We rationalised the usage of a MEK1/2 inhibitor in combination with a PLK1 inhibitor across a series of BC cell lines. We observed synthetic lethality among the aggressive hormone receptor negative lines with higher CEP55 expression compared to normal like and receptor positive lines with lower CEP55 level. The combination synergistically amplified apoptosis of aneuploid population via premature entry of these cells into mitosis in the presence of antimitotic drugs due to exhaustion of CEP55. We have also validated this synergistic effect of MEK1/2 and PLK1 inhibition using xenograft models, results of which imitated the *in vitro* findings.

Conclusions: We propose a novel treatment tactic of MEK1/2 -PLK1 dual combination for selectively targeting CEP55 over-expressing BC in the clinics.

Legal entity responsible for the study: QIMR Berghofer Medical Research Institute

Funding: Cancer Council Queensland (CCQ) and National Health & Medical Research Council

Disclosure: All authors have declared no conflicts of interest.

1662P Synergistic antitumor effects of OT-101 (trabedersen), a transforming growth factor-beta 2 (TGF-β2) antisense oligonucleotide (ASO) and chemotherapy in preclinical tumor models

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Background: Overexpression of TGF-β2 has been implicated in the malignant progression of tumors by inducing immunosuppression, proliferation, angiogenesis and

metastasis. OT-101 (Trabedersen) is a phosphorothioate ASO designed to specifically target human TGF-β2 mRNA. Herein, we report the synergizing effect of OT-101 with chemotherapy in multiple human tumor xenograft models for further exploration of clinical combination strategies.

Methods: OT-101 was administered as single agent (1-64 mg/kg, qdx3/wk or qdx21) and in combination with Gemcitabine (GEM, 15 mg/kg, qdx2/wk), Dacarbazine (DTIC, 1-10 mg/kg, qdx4/wk) or Paclitaxel (PTX, 10 mg/kg, qdx5) to nude mice (10/subgroup) bearing either (i) orthotopic human L3.6pl pancreatic cancer (PAC), (ii) human metastatic C8161 melanoma, (iii) SC glioblastoma (U87) or (iv) SC ovarian (SKOV-3) tumors. Mice were monitored for adverse effects, body weight loss, tumor size and survival outcome. Lymph node and liver surface and micro-metastases as well as size and weight of the pancreatic tumors were determined. Tumor sections were stained with anti-BrdUrd and CD31 antibodies to determine tumor cell proliferation and vascularization, respectively.

Results: OT-101 significantly reduced tumor growth ($p = 0.0084$), lymph node metastasis ($p = 0.023$), and tumor angiogenesis ($p < 0.0001$) versus untreated control in the PAC model. OT-101 demonstrated synergy in tumor growth inhibition and increased survival in human malignant melanoma (C8161, $p = 0.038$, vs. DTIC alone), glioblastoma (U87, $p = 0.001$ vs. PTX) and ovarian (SKOV-3, $p < 0.05$ vs. PTX) cancer models when combined with either DTIC (C8161) or PTX (U87 and SKOV-3). No synergy was observed with GEM (PAC). The combination regimen tested was effective and tolerable. Significant antitumor activity was achieved at HED of 80 mg/m^2/day which is well below the optimized clinical dose used for IV infusion of patients at 140 mg/m^2/day.

Conclusions: The preclinical data laid the groundwork for establishing combination therapies in the clinic. Of interest is the preferential synergy between OT-101 and PTX or DTIC, but not with GEM.

Legal entity responsible for the study: Autotelic Inc

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1663P Targeting thioredoxin reductase 1 in novel combination therapies in p53 mutant triple negative breast cancer

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Background: The TP53 gene is frequently mutated in human cancers including triple negative breast cancers (TNBCs) (~84% patients). Although TP53 mutation is the only oncogenic driver in TNBCs, no targeted therapies for mutant p53 (mtp53) TNBCs are available. We aim to identify novel therapeutic targets and combination therapies for mtp53 TNBCs.

Methods: A large-scale genomic analysis was performed using the TCGA database to analyse the expression of various antioxidant genes in Mt and wild-type (wt) p53 BC cells. Thioredoxin reductase 1 (TrxR1) protein levels and redox activity were measured by western blot and DTNB reduction assay, respectively. Mt and wt p53 cells were treated with gold-based TrxR1 inhibitor and APR-246 and subsequently analysed for cell proliferation, apoptosis, and cell cycle progression. Phospho-histone H3 (pHH3) Ser10 expression was analysed by FACS.

Results: We observed significant upregulation of TrxR1, a redox gene, in mtp53 BC patients compared to wt patients. TrxR1 protein levels and redox activity were higher in mtp53 cells compared to wt cells. Notably, TrxR1 inhibition selectively induced apoptosis in mtp53 BC cells, but not in wt cells. Upon treatment with TrxR1 inhibitor, a significant proportion of mtp53 cells arrested in the G2/M phase with a concomitant increase in pHH3 Ser10, a marker of mitotic chromatin condensation. Thus, TrxR1 inhibition may lead to mtp53 TNBC cell death by causing mitotic catastrophe. APR-246, known to restore wild-type activity of mtp53 in many cancers, alone failed to induce apoptosis in mtp53 BC cells. However, co-treatment of APR-246 with a sub-lethal concentration of TrxR1 inhibitor resulted in a synergistic effect in mtp53 cells.

Conclusions: Inhibiting TrxR1 may represent an effective therapeutic strategy for mtp53 TNBCs. These results warrant the clinical evaluation of a novel combination therapy using APR-246 and TrxR1 inhibitors for mtp53 TNBC patients.

Legal entity responsible for the study: QIMR Berghofer Medical Research Institute

Funding: National Health and Medical Research Council, Australia

Disclosure: All authors have declared no conflicts of interest.

1664P Liprin-α4 could be a potential therapeutic target for pancreatic cancer

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Background: In pancreatic cancer whose microenvironment is extremely hypoxic condition, the analysis of signal transduction under hypoxia is thought to be significantly important. By investigating microarray analysis of pancreatic cancer cultured between under normoxia and under hypoxia, we found that the expression of leukocyte common antigen related (LAR)- interacting protein (liprin)-α4 was extremely increased under hypoxia compared to under normoxia. In the present study, the biological significance of liprin-α4 in pancreatic cancer was investigated and whether liprin-α4 could be a therapeutic target for this refractory cancer was estimated.

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 of liprin-α4 was performed using liprin-α4 siRNA. Expression of liprin-α4 was analyzed by real time RT-PCR, western blot and immunofluorescent staining. Proliferation was estimated by cell count and MTT assay. Invasion was estimated by matrigel invasion assay. Mice xenograft experiments were performed using BALB/c nude female mice. Surgically resected human pancreatic cancer specimens were used for immune staining.

Results: 1) Expression of liprin-α4 was increased in PDAC under hypoxia compared to normoxia. 2) Liprin-α4 suppression decreased invasion through inhibition of endothelial mesenchymal transition in PDAC under hypoxia. 3) Liprin-α4 inhibition decreased proliferation of PDAC under hypoxia *In vitro*. 4) Tumor volume in mice injected with liprin-α4-inhibited PDAC was significantly lower than that in control mice. 5) Signaling from liprin-α4 was through PI3K and MAPK signaling pathways. 6) Relation between hypoxia inducible factor-1α (HIF-1α) expression and liprin-α4 expression was observed by immunofluorescent staining using surgically resected pancreatic cancer specimen.

Conclusions: These results suggest that liprin-α4 which is more expressed under hypoxia, plays pivotal role for inducing malignant phenotype such as proliferation and invasion in pancreatic cancer, and that liprin-α4 could be an effective therapeutic target for pancreatic cancer.

Legal entity responsible for the study: Cancer Therapy and Research, Kyushu University Hospital,

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Disclosure: All authors have declared no conflicts of interest.

1665P Dual targeting of cystathionine β-synthase (CBS) and cystathionine γ-lyase (CSE) by miR-4317 displays a synergistic efficacy in repressing breast cancer progression

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Background: Recently, hydrogen sulphide (H_2S) and its synthesizing enzymes, CBS and CSE, have been casted as pleiotropic regulators in the malignant transformation process. H_2S paradoxically acts as oncogenic mediator in ovarian and liver cancers, and as tumor suppressor in prostate and gastric carcinomas. However, the link between H_2S and Breast cancer (BC) remains unclear. Thus we aimed at unraveling the association between H_2S and its synthesizing enzymes in BC progression. Furthermore, it was essential to evaluate their possible adoption as therapeutic targets in BC through their dual targeting by short non-coding RNAs.

Methods: Breast tissues were collected from 30 BC patients. Ki67 levels were quantified using immunohistochemistry. MDA-MB-231 and MCF7 cells were cultured and transfected with different oligonucleotides and/or treated with NaHS, an exogenous source of H_2S. Total RNA was extracted and quantified by qRT-PCR. Cellular viability, proliferation, and migation were measured using MTT, BrdU and scratch assays respectively. Bioinformatic analysis was performed to predict novel miRNAs that could target both CBS and CSE.

Results: CBS and CSE were significantly upregulated in BC tissues. Patients with high Ki67 scores showed the highest expression levels of CBS and CSE. Knocking down of CBS and CSE using siRNAs resulted in a significant attenuation of different hallmarks of BC. On the other hand, NaHS resulted in an increase in BC progression. miR-4317 was found to putatively target both CBS and CSE oncogenes with high binding scores. Ectopic expression of miR-4317 in BC cell lines resulted in a simultaneous reduction of CBS and CSE transcripts which was associated with a concomitant reduction in cellular viability, proliferation and migration. Finally, co-treatment of miR-4317 and NaHS resulted in abrogation of miR-4317 tumor suppressor activity.

Conclusions: This study showed a marked upregulation of CBS and CSE in BC tissues and characterized them as aggressive oncogenic drivers in BC. Moreover, miR-4317, a novel tumor suppressor in BC, displayed a synergistic effect in halting BC progression via twin-targeting CBS and CSE and diminishing H_2S levels in BC cell lines.

Legal entity responsible for the study: German University in Cairo

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1666P Met/Axl system as a dual target in the mesothelioma pathway and invasiveness

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Background: Malignant pleural mesothelioma is an aggressive and highly lethal disease. Conventional chemotherapies and radiation therapy have limited efficacy. Many evidences suggest the roles of receptors tyrosine kinase (RTKs) in mesothelioma pathogenesis, in particular epidermal growth factor (EGFR), Met and Axl. Axl activation is involved in proliferation and inhibition of apoptosis, and its over-expression represents a key molecular determinant underlying the development of acquired resistance to targeted anticancer agents.

Methods: Different histological types, epithelioid, sarcomatoid and mixed, of human mesothelioma cell lines were used. Protein levels of Met, Axl and its ligand, growth arrest-specific 6 (Gas6) were evaluated by Western Blot analysis. We conducted *in vitro* treatments with different doses of Foretinib, dual inhibitor of Met and Axl, in order to demonstrated the variation of cell proliferation and migration through MTT and Colony Forming Assay at the range dose 0.5-1 μM of Foretinib. Lastly, the rate of cell apoptosis was quantified by flow cytometry.

Results: The presence of Met, Axl and Gas6 proteins were found in all cell lines analyzed with different expression pattern. The dose escalation of Foretinib from 0.01 μM to 2 μM strongly inhibited cell proliferation and migration of mesothelioma cell lines. Treatment with Foretinib (at the dose 0.5 μM and 1 μM), determining a significantly increase of apoptosis rate (up to 50%) in specific histological type suggesting a different cell sensibility.

Conclusions: The co-activation of MET and AXL in mesothelioma cell lines suggests that these kinases could serve as novel therapeutic targets. MET and AXL inhibitors could be used as novel anticancer therapies influence clinically meaningful end points including metastatic recurrence and survival in the majority of tumour types.

Legal entity responsible for the study: University of Campania "Luigi Vanvitelli"

Funding: Associazione Italiana per la Ricerca sul Cancro (AIRC)

Disclosure: All authors have declared no conflicts of interest.

1667P Targeting CXCR4 and FAK in non-small cell lung carcinomas with co-inactivated p53 and PTEN tumor suppressors

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Background: In this study we evaluated potential of targeting CXCR4 and focal adhesion kinase (FAK) in suppressing metastatic spread of p53/PTEN deficient non-small cell lung carcinomas (NSCLCs).

Methods: We first examined the invasive characteristics of NSCLC cells with suppressed p53 and PTEN activity using wound healing, gelatin degradation and invasion assays. Namely, NCI-H460 cells with applied pharmacological inhibition of wild type p53 and PTEN activity (NCI-H460$^{p53-/PTEN-}$) were analyzed along with COR-L23 cells that have intrinsically inactive both tumor suppressors. Further, changes in the expression of CXCR4 and FAK were evaluated by RT-qPCR and Western Blot analysis. Finally, we tested the ability of CXCR4 and FAK inhibitors (WZ811 and PF-573228, respectively) to suppress the migratory and invasive potential of p53/PTEN deficient NSCLC cells, in vitro and in vivo using orthotropic metastatic lung carcinoma mouse model.

Results: Our results showed that cells with mutually inactive p53 and PTEN have significantly increased migratory and invasive potential. Such invasive phenotype is associated with hyperactivation of CXCR4 and FAK and their downstream AKT and ERK signaling pathways. Treatments with WZ811 and PF-573228 significantly reduced migratory and invasive capacity of NCI-H460$^{p53-/PTEN-}$ and COR-L23 cells that was accompanied by the downregulation of AKT signaling. In addition, these two inhibitors showed trend to improve survival of SCID mice with orthotopicaly inoculated COR-L23 cells that extensively invaded lung parenchyma and developed distant metastases compared to NCI-H460 derived tumors.

Conclusions: Overall, we demonstrated that p53/PTEN deficient NSCLCs have extremely invasive phenotype and provided a rationale for the use of CXCR4 or FAK inhibitors for the suppression of NSCLC dissemination.

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Disclosure: All authors have declared no conflicts of interest.

1668P Pin1 protein: A druggable target in high grade serous ovarian cancer

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Background: Epithelial Ovarian cancer (EOC) is the 5th leading cause of cancer death in the USA and the High Grade Serous-EOC is the most common and aggressive type characterized by mutations in the p53 gene (>90%). Pin1 has been demonstrated to activate a mutant p53 transcriptional program. It binds specific phosphoSer/Thr-Pro-motifs and catalyses the cis/trans conformational switch of target proteins. In HGS-EOC, Pin1 is overexpressed in about 50% of cases suggesting that it may be a potential therapeutic target. The Pin1 inhibition affects cellular proliferation, migration, invasion, new angiogenesis and apoptosis suggesting a pivotal role in cancer. Nevertheless, there are still deficiencies in producing Pin1 ligands: Pfizer has reported inhibitors that have poor permeability and low efficacy. Here, it is reported that the encapsulation of these inhibitors in liposomes increases the cytotoxic activity on ovarian cancer cells.

Methods: The inhibitor was encapsulated in ionisable cyclodextrins via a pH gradient. PEG-liposomes were prepared using different molar ratio of cholesterol and lipids. Cell viability was tested with an MTT-like assay. The liposome characteristics were evaluated by DLS and zeta potential. The loading efficiency of drug was calculated via UV-Visible method and the release with a dialysis membrane.

Results: Pegylated liposomes of about 100 nm were synthesized for the encapsulation of drug. This complex has a promising loading efficiency and release rate. These characteristics allow an efficient delivery in different ovarian cancer cells line achieving the IC50 values in the low micromolar range. Instead, inhibitor alone did not change the cell viability.

Conclusions: In summary, we have created a new formulation of Pin1 liposomal inhibitor that can be used to kill ovarian cancer cells. Therefore, for further application in vivo, the inhibitor retention would enhance antitumor efficacy. In fact, the liposome system could have a high concentration in the tumour, thanks to enhanced permeability and retention effect, overtake the tumoral barrier and represents an option for the therapy of ovarian cancer.

Legal entity responsible for the study: Graduate School in Chemistry - University of Trieste

Funding: AIRC - Associazione Italiana Ricerca sul Cancro

Disclosure: All authors have declared no conflicts of interest.

1669P RalB GTPase: A potential novel target for RAS mutant colorectal cancer

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Background: Colorectal cancer is the 3rd most common cancer in the UK, with around 40,000 new cases diagnosed annually. CRC patients have a 5-year overall survival rate of < 10% and more than 50% will die of metastatic disease. Intrinsic or acquired resistance to chemotherapeutic drugs is a major problem in CRC and developing an effective treatment strategy is therefore of the utmost importance. CRC cases harbouring *RAS* mutations (>50% cases) are associated with poor prognosis; this mutation has proven to be an important predictive factor for response to EGFR targeted therapies. Failure to target the *RAS* oncogene has resulted in a concentrated effort to discover targets within the downstream components of this pathway. In this study, we evaluate the roles of the small GTPases, RalA and RalB, as novel targets in *RAS* mutant (MT) CRC. The RALGDS/RAL pathway constitutes a RAS effector pathway and mediates cell survival, proliferation and tumorigenesis. RalB in particular contributes to cell survival through TBK1 signalling.

Methods: We used an siRNA-based approach silencing RALA and RALB both individually and simultaneously in a panel of *KRAS*MT and WT cells with and without the addition of the MEKi AZD6244 (Selumetinib). Knockdown efficiency and subsequent signalling events were assessed by western blotting. Flow cytometry and MTT assays were used to measure cell death and cell viability respectively. Connectivity mapping using data from microarray experiments was used to identify drugs mimicking the phenotype observed with siRALB, subsequently leading to the investigation of a TBK1 inhibitor which is currently ongoing.

Results: We found that silencing RALB but not RALA, led to the greatest amount of cell death in *RAS*MT but not WT CRC cells. In addition, a significant increase in cell death was observed when RALB silencing was combined with MEK inhibition. Cell death was found to be mediated by Caspase 8 and involved an upregulation of death receptor 5

(DR5). Furthermore, TBK1 inhibition was found to mimic the phenotype observed with siRALB.

Conclusions: RalB but not RalA, is associated with cell survival and may contribute to drug resistance in *RAS*MT CRC. Thus, the development of novel RalB-specific therapies may lead to new treatment strategies for *RAS* MT CRC.

Legal entity responsible for the study: Queen's University Belfast

Funding: Queen's University Belfast, Cancer Research UK

Disclosure: All authors have declared no conflicts of interest.

1670P Serial genotypic characterization of circulating tumor cells (CTCs) in patients with metastatic castration resistant prostate cancer (mCRPC) undergoing treatment with abiraterone acetate (abi) or enzalutamide (enza)

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Background: While enza and abi have substantially improved outcomes for patients (pts) with mCRPC, de novo and acquired resistance mutations are increasingly recognized.

Methods: Pts receiving abi or enza in the course of routine clinical care were consented for blood collection at weeks 0, 4, 8 and 12 of therapy, and at the time of progression (based on Prostate Cancer Working Group 3 [PCGW3] criteria). CellSearch was used for CTC enumeration; individual cells were isolated and subsequently classified for EpCAM and C45 positivity. RNA sequencing (RNA-seq) was performed on pools of up to 10 CTCs.

Results: Amongst 36 pts enrolled, median age was 71 (range, 54-84) and median PSA was 21.9 ng/dL (range, 0-918.3). Regarding treatment, 21 pts received abi and 15 received enza. By PCWG3 criteria, 23 pts met the definition of progression on abi or enza. Mean/median CTC count was 158/5 (IQR 25%-75%, 0-15). On RNA-seq of CTCs collected at the time of progression, AR was the most mutated gene followed by ATRX, GNAS, FOXA1, KMT2A and CNOT1. Several deleterious mutations in the DNA damage response genes were noted including frameshift mutations in PRKDC, MSH2 and MLH1. Differential gene expression analysis between abi/enza sensitive and abi/enza resistant samples revealed 2100 differentially regulated genes in drug-resistant CTCs. Ingenuity pathway analysis was used to identify pathways altered due to differential regulation of these genes. Among these pathways, TGFβ and CCDN1 signaling were found to be significantly up-regulated in drug resistant CTCs. In vitro enza-resistant models will be presented, offering validation of our clinical findings.

Conclusions: RNA-seq of CTCs representing abi/enza sensitive and resistant states can identify potential mechanisms of resistance. Therapies targeting the downstream signaling mediated by CCND1, such as CDK4/6 inhibitors (e.g., palbociclib or ribociclib), could avert resistance. Targeting TGFβ, another putative mediator of resistance, may be warranted.

Legal entity responsible for the study: Sumanta Kumar Pal

Funding: Janssen Pharmaceutical Company

Disclosure: J. Patel, B. Foulk, V. Bhargava, D.A. Smirnov: Working for Janssen Pharmaceutical Company All other authors have declared no conflicts of interest.

1671P A novel circulating cell free DNA-based assay can predict tumor response to systematic chemotherapy

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Background: Although circulating cell-free DNA (cfDNA) in blood is being touted as a frontier noninvasive approaches, its clinical utility still remains questionable. The purpose of this study was to compare the efficacy of cfDNA by comparing with blood CEA levels and radiological evaluation in patients with unresectable metastatic colorectal cancer (mCRC) during treatment of systemic chemotherapy.

Methods: In this study, 12 patients with mCRC who were intended to receiving systemic chemotherapy were enrolled. Methylation status of CpG sites, considered as cancer-specific alteration, and concentration of cfDNA were evaluated from blood plasma obtained before administration of systemic chemotherapy in each treatment cycle. To analyze aberrant cancer-specific methylation, we modified the highly sensitive assay for bisulfite DNA (Hi-SA) followed by fluorescence-based PCR, as reported previously (JNCI 2009). Our modified methodology can detect 8 loci of target promoters, therefore methylation score (MS) could be ranged from 0 to 8 at a given time.

Results: Of the 12 patients enrolled, 10 patients experienced radiological progressive disease (PD). Plasma MS was significantly increased before radiological PD in 8 of 10 patients with PD. Thus MS had the median lead time of 73 days (range: 0-231 days) before documentation of radiological PD. In contrast, serum CEA level could predict PD only in the 2 patients before documentation of their radiological PD. Consequently, plasma MS could predict radiological PD with the median lead time of 9 days (range: 0-21 days) compared with serum CEA. We also examined whether cfDNA concentration level in plasma was associated with radiological PD. Of the 12 patients, only 3 patients increased cfDNA concentration level before radiological PD with the median lead time of 88 days (range; 21-140 days).

Conclusions: Our circulating cell free DNA-based assay is a robust methodology for capturing DNA methylation in circulating cell-free DNA in plasma, and is useful for the early identification of CRC patients that are at risk of developing PD prior to radiographic documentation.

Legal entity responsible for the study: Takeshi Nagasaka

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1672P ctDNA might expand therapeutic options for second line treatment of KRAS mutant mCRC

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Background: KRAS mutations predict failure of anti-EGFR therapies, thus genotyping colorectal cancer (CRC) is crucial for personalized treatments. Cancer heterogeneity hamper the assessment of KRAS mutational status in tumor tissues, leading to the search for alternative sources of cancer genetic information. ctDNA of patients treated with anti-EGFR drugs exhibit pulsatile levels of KRAS mutations, revealing that the CRC genome adapts dynamically to intermittent EGFR blockade. These data support the use of liquid biopsy to monitor the molecular underpinnings of resistance to anti-EGFR agents. Research has been selectively concentrated on the emergence of resistant clones in the blood of patients with wtKRAS CRC as biomarker of anti-EGFR therapy resistance. Conversely our group demonstrated that patients with metastatic CRC harboring mutated primary tumors, thus not candidate to EGFR inhibitors, frequently have wtKRAS circulating tumor cells in blood. To explain the prevalence of wtKRAS clones in these patients, the generation of hypoxia has been suggested. We aimed to determine if anti-angiogenic drugs might drive the biological evolution of mKRAS clones towards a prevalent wtKRAS disease, by ctDNA.

Methods: Ten patients with histologically confirmed mKRAS mCRC candidate to first-line anti angiogenic drugs were prospectively enrolled. To investigate whether wtKRAS clones emerge as dominant under treatments, serial blood draws were performed at baseline and at 3 months months of treatment. Idylla™ (Biocartis) ctKRAS Mutation Assay was used to track KRAS mutational status in serial ctDNA determinations for each patient.

Results: At baseline, KRAS mutational status in ctDNA was found concordant with tumor tissues in all patients analysed. At 3 months,3/10 (30%) of mKRAS CRC patients treated with antiangiogenic drugs switched to wtKRAS ctDNA in peripheral blood.

Conclusions: These preliminary data suggest that patients with mKRAS colon cancer not unfrequently switch to a prevalent wtKRAS disease in course of treatment with anti-angiogenic drugs. if confirmed in a large patients population, these results might shift second-line therapeutic options for KRAS mutant mCRC patients from insufficient to promising.

Legal entity responsible for the study: Paola Gazzaniga

Funding: Merck

Disclosure: All authors have declared no conflicts of interest.

1673P Ex vivo expansion of circulating tumor cells for individualized drug susceptibility in patients with advanced or recurrent oesophageal cancer

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Background: Esophageal cancer (EC) is the eighth most common cancer in the world. The incident rate of EC is significantly high in Asian countries compared to rest of the world. Circulating tumor cells (CTCs) derived from EC have the potential to be precursors of metastasis. It is therefore of paramount interest to isolate and characterize CTCs from EC patients to monitor and detection of recurrence. The aim of present study is to evaluate drug response using patient-derived CTC cultures obtained from EC.

Methods: Custom microfabricated tapered microwells will be integrated with microfluidics to expand CTC clusters without any prior pre-enrichment. The established CTC cluster assay will be used to screen anticancer drugs. The drug concentrations selected will be centered on the IC50 that had previously established for each drug across EC cell lines. Cluster formation in culture will be correlated with overall patient survival. 50 patients with a proven diagnosis of EC attending the Department of Surgical Oncology, Kidwai Institute of Oncology will be enrolled into the study.

Results: Our initial results showed CTC clusters formation in the patients with metastatic EC. This cluster formation was affected by the presence and duration of systemic therapy. We observed a progressive reduction in cluster formation in samples from patients who had undergone increasing longer treatment.

Conclusions: Our result suggests that CTC cluster can be used to rapid evaluation of drug response. We would further use the CTC cluster assay as a potential tool for evaluating patient prognosis during treatment. The study will be employed to determine the drug susceptibility pattern in individual patients and also provide therapeutic choices for personalized treatment.

Legal entity responsible for the study: Kidwai Memorial Institute of Oncology, Institute of Bioinformatics

Funding: Department of Science and Technology, (DST) Government of India

Disclosure: All authors have declared no conflicts of interest.

1674P Exploratory study of CK-M30 and pHH3 expression in Circulating Tumor Cells (CTCs) as biomarkers of docetaxel (DOC) efficacy in metastatic castration resistant prostate cancer (mCRPC)

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Background: A drop in CTCs counts as early as 4 weeks following treatment initiation have been suggested as an indicator of overall survival (OS) benefit. DOC remains a pivotal treatment in mCRPC for which there are no early pharmacodynamic (PD) markers of its activity in patients (pts). CTCs may be used as surrogate tumor tissue to study PD markers of apoptosis (CK-M30) or mitosis arrest (pHH3) in mCRPC pts receiving DOC.

Methods: We conducted a prospective 2-cohort multicenter exploratory study in mCRPC pts progressing by PCWG2 criteria who were eligible for DOC 75 mg/m2. Pts were prescreened using the CellSearch system and selected if CTCs≥5/7.5mLs of blood (Basal 1). A 2nd blood sample (Basal 2) was drawn in eligible pts within 0-7 days prior to C1D1 of DOC and further samples were collected at 8h, 24h, 7d and 21d. Directly conjugated mAb against pHH3 and CK-M30 were used in combination with CellSearch. Statistical analyses were performed to evaluate the baseline and post-treatment variability. Increases in % of biomarker CTC+ greater than the median baseline variability were correlated with achieving a 50% PSA response (PSA50) and OS from DOC start using chi-square and long-rank test, respectively.

Results: 60 mCRPC pts (CK-M30 = 30; pHH3 = 30), 95% ECOG 0-1, 95% and 17% have bone and visceral metastases respectively, received a median of 7 cycles (range 2-10) of DOC. Biomarker results are summarised in Table.

Conclusions: pHH3 in CTC+ may be a potential PD biomarker of a favourable response to DOC treatment.

Legal entity responsible for the study: Spanish National Cancer Research Centre

Funding: None

Disclosure: All authors have declared no conflicts of interest.

Table: 1674P Variability

		Basal 1 (N = 60) Median (Range)	Basal 2 (N = 57) Median (Range)	%marker Corr. Coeff	Post-24h (n = 59) median (Range)	P-value Basal vs post-24h
Cohort CK-M30	CTC/7.5mL	9 (5-1266)	8 (3-863)	0.54 p = 0.763	9 (4-1129)	NS
	CK-M30+	48% (0-76%)	35% (0-100%)		51% (0-100%)	
Cohort pHH3	CTC/7.5mL	10 (5-567)	12 (4-623)	0.98 p < 0.001	9 (3-584)	<0.001
	pHH3+	0% (0-10%)	0% (0-8%)		7% (0-67%)	
Response		N	PSA50	p-value	OS median (CI95%)	p-value
CK-M30+ change 24h	CKM30 + >50%	5	2	NS	24 m (–)	NS
	CKM30 + <50%	25	11		21 m (12-30)	
pHH3+ change 24h	pHH3 + >10%	13	8	0.047	17 m (12-22)	NS
	pHH3 + <10%	16	4		12 m (6-18)	

1675P Risk of recurrence prediction and optimum treatment planning for early stage breast cancer patients: A cost-effective, accurate and broad based solution for Asia

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Background: Current molecular risk stratification tests have helped clinicians to optimize Chemotherapy for early stage breast cancer patients leading to huge savings in treatment costs and improved quality of life. However, current tests are not impactful in the Asia due to the extreme cost-sensitivity of the market. Aim of this study was to develop and validate a cost-effective, broad based and robust test to stratify early stage hormone receptor positive patients based on individual risk of recurrence.

Methods: A retrospective cohort of 300 patients, was used to develop 'CanAssist-Breast'- a Morphometric Immunohistochemistry based test comprising 5 biomarkers plus three clinical parameters (Tumor size, node status and grade) using SVM based algorithm. CanAssist-Breast biomarkers belong to key signaling pathways involved tumor invasion and chemotherapy resistance.

Results: CanAssist-Breast classifies patients into 'low or high' risk of recurrence based on "CanAssist-Breast Score" score. Test validation in a 800+ sample cohort demonstrated that it is useful in both node negative and positive patients, as well as chemotherapy naïve and treated patients. CanAssist-Breast Score, is a strong independent predictor of disease recurrence by multivariate analysis. The majority of patients in 'low risk' had Stage 2, Grade 2/3 disease over Stage 1, Grade 1 disease. Comparison with commonly used prognostic tools including Ki67, the online tool PREDICT and Oncotype Dx showed that CanAssist-Breast test was superior in determining prognosis.

Conclusions: CanAssist-Breast is a low-cost, prognostic and chemotherapy predictive test to predict risk of recurrence and enable optimal treatment planning in patients with early stage Breast Cancer in Asia.

Legal entity responsible for the study: DCGI registered Ethical Committee based in Bangalore, India.

Funding: Onco Stem Diagnostics Private Limited

Disclosure: M.M. Bakre: OncoStem Diagnostics is start-up biotechnology company privately funded by venture capitalist. The retrospective, non-interventional, observational study was approved by DCGI registered Ethical Committee based in Bangalore, India. All other authors have declared no conflicts of interest.

1676P Comparison of progression-free survival (PFS) on comprehensive multiplatform profiling-guided therapy to PFS on prior therapy: A pooled analysis from 4 contemporary prospective studies

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Background: It is expected that the progression-free survival (PFS) for patients with refractory cancers will decline over subsequent lines of therapy. Patients with refractory metastatic cancer have previously been shown to derive some clinical benefit from comprehensive multiplatform profiling (CMP) of tumor tissue. Data from four

independent physician-led prospective and prospective/retrospective studies was pooled in an exploratory manner to determine if PFS was improved when patients were treated with molecular profiling-guided therapies compared to PFS on the prior therapies.

Methods: Tumor tissue specimens from 202 patients were submitted for CMP to a certified referral laboratory (Caris Life Sciences, USA) between March 2010 and December 2016. Treatment selections were based on predictive biomarker status associated with agents with potential clinical benefit. Clinical benefit was defined as a PFS ratio (= PFS upon treatment according to CMP/PFS on the prior therapy) ≥ 1.3.

Results: As of December 2016, 157 of 202 (77.8%) profiled patients were treated according to the predictive results, of whom 140 were evaluable. Patients had received a median of three prior therapies (range 1-12). The most common tumor types were breast (n = 35), colorectal (n = 14), non-small cell lung (n = 11) and gastric cancer (n = 9). A median PFS of 120.0 days was observed with CMP-directed therapies compared to 89.5 days for prior therapies (HR = 0.70, p = 0.012). Seventy-three of 140 patients (52%) had a PFS ratio ≥ 1.3. Over 70% of treated patients received chemotherapy alone, while 21% of patients received targeted therapies, either alone or in combination with chemotherapy or hormone therapy.

Conclusions: Contrary to the expected decline in PFS, patients had a better outcome when treated with CMP-guided treatments. This was interestingly driven by the precision use of available chemotherapeutic resources rather than sometimes inaccessible targeted therapies. Further prospective trials in specific tumor types may help to highlight particular patient populations who might benefit most from CMP guidance.

Legal entity responsible for the study: Günther Gastl

Funding: None

Disclosure: A. Seeber: Consultant for Caris Life Sciences All other authors have declared no conflicts of interest.

1677P Effect of enoxaparin, omeprazole, gemcitabine and bortezomib in refractory patients

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Background: Repurposing drugs and immunogenic chemotherapy for cancer is an emerging field, especially the combination of drugs with validated data. Several studies have shown that enoxaparin, omeprazole, gemcitabine and bortezomib have immunomodulatory properties that synergize with several chemotherapeutic protocols and decrease chemoresistance in several tumors. We treated refractory patients with ECOG=0 with this combination. We demonstrated significant clinical response that correlated with the immune response after 2 months of weekly treatment.

Methods: CICS IRB approved this protocol and inform of consent was signed. We included 10 patients, median age 45 years old of each tumor with at least 2-4 relapses. The patients receive intravenous 0.5 gr/m^2 of gemcitabine, 3.5 mg of bortezomib, 80 mg of omeprazole and enoxaparin was administrated subcutaneously in the area with more tumor activity according with the CT SCAN, Granzyme B ELISPOT and cytokine ELISA that were performed before, during and after the treatment. We analyzed the data with prism graph pad and by multivariate analysis using SAS/STAT.

Results: We had a significant correlation between increased levels of CD8 cells (p = 0.0003) and PFS in the 100% of the patients. The cytokines measured were downregulated after the treatment with significant correlation with IL-6 (p = 0.001), IL-8 (p = 0.001), IL-18, (p = 0.01) and TNF alpha (p = 0.005) and CR after the third CT scans. The laboratory tests before, during and after the treatment did not demonstrate clinical significant toxicity.

Conclusions: The results obtained in this pilot study gave relevant data to prepare a phase I trial. We conclude that this combination is feasible to overcome chemoresistance and improve the anti-tumor immune response by CD8 cells and decreasing cytokines associated with tumor progression.

Legal entity responsible for the study: Centro de Investigacion de cancer en Sonora (CICS) campus Ciudad Obregon, Sonora, Mexico.

Funding: Fundacion del Centro de Investigacion de cancer en Sonora campus Ciudad Obregon

Disclosure: The author has declared no conflicts of interest.

1678P A new chemotherapy-based combination to prevent osteosarcoma progression

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Background: Despite the intensification of chemotherapy regimen, 5 years survival rates for patients with metastatic or relapsed osteosarcoma (OS) remains of 20%. The secreted factor netrin 1 (Nt1) is overexpressed in many human cancers to block apoptosis. Recent studies showed that blocking Nt1 interaction with its receptors potentiates chemotherapy efficacy suggesting that combining chemotherapies with Nt1 interference could be a promising approach for chemoresistant tumors like OS.

Methods: Analyses of the ATGSarc database (http://atg-sarc.sarcomabcb.org/), indicate that Sarcoma with complex genomic (SCG) with a higher expression of Nt1 have a poorer outcome (p < 0.002). In addition, q PCR performed on human sarcomas samples showed that Nt1 is higher expressed in OS compared to other SCG (7.75 fold increase - p < 0.02). These data indicated that Nt1 could be a potential target for OS treatment. Thus, we evaluated the antitumoral effects of anti Nt1 monoclonal antibody (aNt1) combined to doxorubicin (Dox) in a rat syngeneic and metastatic OS model. In this model, treatments were administered either on progressive OS or post operatively to prevent OS relapse. At the end of the experiments tumors and lung were collected for IHC analyses.

Results: As pre operative treatment, Dox/aNt1 combination caused a marked delay in OS progression (median end point reached at day 17 and day 22 respectively in Dox and Dox/aNt1 group, (p < 0.02) and dramatically slowed down metastatic spreading: lung metastases (d > 5mm) were found respectively in 75% and 17% of Dox and Dox/aNt1 treated rats As post operative treatment, Dox/aNt1combination significantly increased animals survival (median end point reached at day 15 and day 21 respectively in Dox and in Dox/aNt1 group; (p < 0.02). Moreover, 19 days after tumor resection, 10% of the Dox treated tumors hadn't relapsed versus 40% in the Dox/aNt1 treated group. A variation in tumor vascular density caused by the treatment was found in the Anti Nt1 treated groups as shown by CD146 staining.

Conclusions: Our study reporting the antiproliferative and antimetastatic effects and of Dox/aNt1 Combination in OS indicate that this combined treatment could be a way to overcome OS chemoresistance.

Legal entity responsible for the study: Dutour Aurélie

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1679P Mutant KIT translocates into the nucleus and induces NFKBIB expression that leads to KIT expression in imatinib-resistant gastrointestinal stromal tumors

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Background: Gastrointestinal stromal tumor (GIST) is a dominantly mutant KIT-driven tumor. Prolonged tyrosine kinase inhibitor (TKI) treatment may result in a resistant phenotype through acquired secondary KIT mutation. Increasing evidences show that membrane-bound receptors, as EGFR, can translocate into the nucleus, mediate genes expression, and lead to tumor survival and drug resistance. However, it's barely known the nuclear role of KIT in GIST.

Methods: In this study, two imatinib (IM)-resistant GIST cell lines, GIST48 and GIST430, were used as a model.

Results: In this study, we first showed that KIT is distributed both in the cytoplasm and the nucleus in IM-resistant GIST cells. Using ChIP-seq and ChIP assay, we identified that nuclear KIT bound to the *NFKBIB* promoter region and regulated its expression. The expression levels of NFKBIB and phosopho-KIT were significantly correlated with NCCN-risk category in surgically resected GISTs stained by immunohistochemistry. The cell viabilities were inhibited as accompanying with KIT reduction in GIST cells while NFKBIB was silenced or RELA was overexpressed. Moreover, RELA was activated, translocated into the nucleus, and bound to *KIT* promoter region in NFKBIB-silenced or RELA-overexpressed GIST cells. Valproic acid, acted as a NFKB inducer, could induce RELA nucleus translocation and binding to *KIT* promoter region that led to the reduction of protein and RNA expression level of KIT and the cell viabilities of GIST cells. Furthermore, the combination of IM with low-dose valproic acid showed synergistically inhibitory effect on cell viabilities of GIST cells and comparable effects on reducing phospho-KIT level and inhibiting tumor growth as high-dose valproic acid did in GIST430 xenograft model.

Conclusions: Taken together, we first demonstrated that phosphorylated KIT could translocate into the nucleus and drive itself expression in IM-resistant GIST cells through mediating NFKBIB expression. In addition, our findings identified a novel and druggable KIT-NFKBIB-NFKB regulatory axis that provides a new insight on tumorigenesis and therapeutic option for IM-resistant, mutant KIT-expressing GISTs.

Legal entity responsible for the study: National Institute of Cancer Research, National Health Research Institutes, Tainan, Taiwan

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1680P Reversion of epithelial–mesenchymal transition (EMT) as a mechanism of action of cabazitazel in castration-resistant prostate cancer

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Background: The epithelial to mesenchymal transition (EMT) process is involved in *de novo* and acquired resistance to hormone-therapy and docetaxel (D) in metastatic castration resistant prostate cancer (mCRPC). Cabazitaxel (CZ) it active after D-progression and prior second-line hormone-therapies. Here we investigated the differences between CZ and D resistance related to the EMT phenotype acquisition and its potential clinical value.

Methods: D and CZ resistant (R) cells lines were derived from parental DU-145 and PC-3. Cell line Molecular characterization was performed using Affymetrix GeneChip Human Gene 2.0 ST microarrays. Gene expression analysis was performed by quantitative real-time PCR in cell lines and in FFPE tumors from mCRPC treated with CZ. Protein levels were measured by Western Blot. Cell migration was assessed using the Cultrex cell migration kit (Trevigen) andcell viability by MTT assay. Gene inhibitory experiments were performed by siRNA transfection.

Results: Microarray data, pathway analysis and EMT gene data *in silico* validation showed that EMT occurred in both D-R and CZ-R cells, being *ZEB1* one of the top deregulated genes. However, we identified 55 EMT genes differentially deregulated between D-R and CZ-R vs parental cells. Among them *CDH1*, and *ESRP1* (lost in D-R but maintained in Cz-R), and *AXL* (overexpressed in D-R and downregulated in CZ-R). D-R cells presented a more pronounced mesenchymal phenotype (morphology, higher migration and lower proliferation rates, higher expression of EMT markers at mRNA and protein level) than CZ-R. Dose-response experiments showed that CZ induced *CDH1* and *ESRP1* expression in different cell lines models. *ZEB1* inhibition reverted D- resistance, but not CZ-resistance, and restored *ESRP1* expression in D-R cells. In 29 CRPC patients treated with CZ, low level of expression of ESRP-1 in tumor correlated with a better PSA-PFS (6.2 vs 2.7 months, P = 0.006; HR: 0.31 P = 0.009) and radiological PFS (7.9 vs 3.3 months, P = 0.047; HR: 0.39 P = 0.055) and the EMT phenotype was not associated to resistance.

Conclusions: The reversion of EMT phenotype, trough induction of *CDH1* and *ESRP1*, may be a novel mechanism of action of CZ, which may explain its activity in patients progressing to prior therapies in CPRC.

Legal entity responsible for the study: Hospital Clínic of Barcelona

Funding: Sanofi-Aventis

Disclosure: All authors have declared no conflicts of interest.

1681P Globally optimizing therapeutic combinations against bortezomib-resistant multiple myeloma using a quantitative parabolic optimization platform (QPOP)

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Background: Multiple myeloma is an incurable hematological malignancy that relies on drug combinations as first and secondary lines of treatment. The inclusion of proteasome inhibitors, such as bortezomib, into these drug combination regimens has improved median survival. Resistance to bortezomib, however, is a common occurrence that ultimately contributes to treatment failure. Thus, there remains a need to identify improved drug combinations that may serve as later lines of treatment.

Methods: We have developed the quantitative parabolic optimization platform (QPOP) to optimize drug combinations against bortezomib-resistant multiple myeloma. By mapping phenotypic output data to parabolic response surfaces, QPOP is able to deterministically optimize drug combinations as well as drug dosages.

Results: We have successfully identified potential optimal drug combinations against bortezomib-resistant RPMI 8226 (P100v) cell line as projected via QPOP, with these combinations exhibiting synergistic response surface maps. The drug combinations displayed lower half-maximal inhibitory concentrations (IC_{50}) *in vitro* as compared to single drug administration. While QPOP does not rely on molecular mechanism prediction, the identified optimal drug combinations can reverse DNA hypermethylation and silencing of tumor suppressors that occurs following acquired bortezomib-resistance. Prolonged survival of P100v tumor-bearing mice was observed when these optimized combinations were validated *in vivo*, further highlighting the importance of treating *in vitro* and *in vivo* as two separate entities. Moreover, the drug combination is broadly effective across a range of primary multiple myeloma patient samples.

Conclusions: These results collectively show that QPOP is a robust platform that is able to eradicate the bortezomib-resistant clones of multiple myeloma. Beyond bortezomib-resistant multiple myeloma, global optimization of drug combinations by QPOP can serve to improve drug combination design across a range of other cancers and diseases through a continuous optimization process across the entire drug development pipeline.

Legal entity responsible for the study: Masturah Rashid

Funding: National Research Foundation Cancer Science Institute of Singapore RCE Main Grant

Disclosure: All authors have declared no conflicts of interest.

1682P Compartmentalized activities of the pyruvate dehydrogenase complex sustain lipogenesis in prostate cancer

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Background: Metabolism in cancer serves to provide energy and key biomolecules that sustain cell growth, a process that is frequently accompanied by decreased mitochondrial use of glucose. Importantly, metabolic intermediates including mitochondrial metabolites are central substrates for post-translational modifications at the core of cellular signalling and epigenetics. However, the molecular means that coordinate the use of mitochondrial metabolites for anabolism and nuclear protein modification are poorly understood.

Methods: We constructed prostate specific Pten; Pdha1 double knockout mice by crossing transgenic mice with flox elements flanking exon 8 of Pten gene and exon 4 and exon 5 of Pdha1 gene. Gene expression profiling analysis and metabolic analysis between Pten; Pdha1 double knockout and Pten knockout tumours were performed to investigate the metabolic pathways altered upon Pdha1 inactivation. Lipidomics analysis between these two genotypes of tumours were performed to reveal the difference on the lipid and cholesterol ester species in response to Pdha1 inactivation.

Results: We found that genetic and pharmacological inactivation of Pyruvate Dehydrogenase A1 (PDHA1), a subunit of pyruvate dehydrogenase complex (PDC) that regulates mitochondrial metabolism inhibits prostate cancer development in different mouse and human xenograft tumour models. Intriguingly, we found that lipid biosynthesis was strongly affected in prostate tumours upon PDC inactivation. Mechanistically, we found that nuclear PDC controls the expression of Sterol regulatory element-binding transcription factor (SREBF) target genes by mediating histone acetylation whereas mitochondrial PDC provides cytosolic citrate for lipid synthesis in a coordinated effort to sustain anabolism. In line with the oncogenic function of PDC in prostate cancer, we find that PDHA1 and the PDC activator, Pyruvate dehydrogenase phospatase 1 (PDP1), are frequently amplified and overexpressed at gene and protein level in these tumours.

Conclusions: Taken together, our findings demonstrate that mitochondrial and nuclear PDC sustains prostate tumourigenesis by controlling lipid biosynthesis thereby pointing at this complex as a novel target for cancer therapy.

Legal entity responsible for the study: Molecular Oncology, Institute of Oncology Research

Funding: IBSA foundation

Disclosure: All authors have declared no conflicts of interest.

1683P Metabolomics in cancer cachexia

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Background: Cancer cachexia (CC) is a frequent unmet medical need. CC affects up to 80% of cancer patients, and it is indirectly responsible for at least 20% of cancer deaths. The pathophysiology is characterized by a variable combination of reduced food intake and abnormal metabolism, including systemic inflammation and negative protein and energy balance. Despite its high clinical significance, definite diagnostic criteria of cachexia are lacking. The 'omics' technologies provide a global view of biological systems. Among these, blood-based metabolomics is a promising method for cachexia study.

Methods: This study is part of a pilot, observational, cross-sectional, case-control, hypothesis generating, IRB-reviewed, research project. Objective: discovery and selection of biomarkers of cancer cachexia. Anthropometric, clinical and biochemical data from consenting eligible cancer patients were collected. Plasma proteome was assessed by 2D gel electrophoresis and MALDITOF mass spectrometry. Metabolomics was evaluated by means of a multiplatform non-targeted approach of plasma samples (LC –MS, GC-MS and CE-MS), to increase metabolite coverage. Data were analysed by univariate

and multivariate methods, using principal component analyses and error adjustments for multiple comparisons.

Results: from metabolomics study are shown. Subjects: 15 cancer (ca) patients (pts), distributed as follows: Cachexia (CX): 8 pts (male:female 7:1; pancreatic ca: 3, melanoma: 3, biliary duct ca: 2); control (CN): 7 pts (M:F 6:1; colon ca: 1, esophageal ca: 1, gastric ca: 2, pancreatic ca: 1, melanoma: 1, sarcoma:1). Median age: CX 62 y (36-81), CN 64 y (48-80); median body mass index: CX 20 Kg/m2 (17-27), CN 25 Kg/m2 (21-27); median albumin: CX 3.4 mg/dL (2.1-4.1), CN 3.9 mg/dL (3.5-4.8). A total of 89 metabolites (Mbl) were significantly altered in CX pts. The Mbl with highest increase was cortisol (fold change 1.67, $p = 0.03$). The largest affected group of Mbl was 'amino acids and derivatives', all decreased. Glycerophospholipids, sphingolipids, steroid derivatives, fatty acids, aldehydes, phenylacetamides, carboxilic acids and derivatives, and indoles were also decreased.

Conclusions: These finding suggest that plasma amino acids and lipids profiling has great potential for improving cachexia cancer screening and diagnosis, and understanding disease pathogenesis. Of note, the increased values of cortisol should lead us to revisit the use of glucocorticoids in this setting. Substitutive therapy for some of the observed deficiencies might deserve clinical exploration.

Legal entity responsible for the study: Instituto de Investigación Sanitaria Hospital 12 de Octubre

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Disclosure: All authors have declared no conflicts of interest.

1684P Association between the Dietary Inflammatory Index (DII), urinary enterolignans and C-reactive protein in the National Health and Nutrition Examination Survey-2003-2008

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Background: Enterolignans are important biomarkers of microbiome diversity. Higher levels, indicating greater diversity, have been shown to reduce cancer risk. Diet and inflammation have been shown to play a role in maintaining microbiome diversity. This study examined whether inflammatory potential of diet, as measured by the Dietary Inflammatory Index™ (DII) has an impact on levels of urinary enterolignans in the National Health and Nutrition Examination Survey (NHANES) 2003-2008. We also carried out validation of the DII with C-reactive protein (CRP).

Methods: Data came from NHANES 2003-2008. Enterolignans (enterodiol and enterolactone) and CRP were assayed from urine and serum specimens, respectively. DII scores were calculated from food intakes assessed using 24-hour dietary recalls and expressed per 1,000 calories consumed. Associations were examined using survey-based multivariable linear and logistic regression.

Results: After adjustment, higher DII scores (i.e., relatively more pro inflammatory) were associated with lower levels of creatinine normalized enterodiol ($b_{DIIquartile4vs1} = -1.22$; 95% CI = -0.69, -1.74; $P_{trend} = <0.001$) and enterolactone ($b_{DIIquartile4vs1} = -7.80$; 95% CI = -5.33, -10.26; $P_{trend} = <0.001$). A positive association also was observed when enterolignans were dichotomized at the 90th percentile value. In this same sample DII scores also were associated with CRP $\geq$3mg/l ($OR_{DIIcontinuous}$=1.12; 95% CI = 1.05, 1.19).

Conclusions: In these NHANES data, there was an association between DII and enterolignans. This study also provided a successful construct validation of the DII using CRP in a nationally representative sample. Using enterolignans as a proxy for gut microbiome, these results indicate that diet-associated inflammation modifies gut diversity.

Legal entity responsible for the study: University of South Carolina

Funding: NIH.

Disclosure: N. Shivappa, M. Wirth, J. Hebert: Dr. James R. Hébert owns controlling interest in Connecting Health Innovations LLC (CHI), a company planning to license the right to his invention of the dietary inflammatory index (DII). Drs. Nitin Shivappa and Michael Wirth are employees of CHI. All other authors have declared no conflicts of interest.

1685P Fullerenol/iron nanocomposite modulates doxorubicin-induced cardiotoxicity

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Background: Doxorubicin is a first line cancer chemotherapeutic. Unfortunately, its clinical use is limited by its cardiotoxicity. It is known that iron overload aggravates anthracycline toxicity. Fullerenol is a 1 nm size molecule and in aqueous solutions is in the form of polyanionic nanoparticles, which enables them to serve as a good carrier of positively charged ions such as Fe^{2+}. Fullerenol's antioxidant activity through scavenging free radicals has already been proved in different biological systems.

Methods: The aim of our study was to investigate the effects of the fullerenol/iron nanocomposite as a pretreatment to doxorubicin on the rat's heart in comparison to doxorubicin alone. After the 24h-treatment, adult male Wistar rats were sacrificed and hearts were collected for ultrastructural and qRT-PCR analysis. Considering the ability of doxorubicin to induce oxidative stress, and the fullerenol's capability to mitigate it, we had chosen to monitor gene expression of enzymes involved in antioxidant defense.

Results: Ultrastructural study revealed that in the group pretreated with the nanocomposite prior to doxorubicin application cardiomyocytes were with preserved morphology and the structure of intercalated discs. On the other hand, the heart tissues of animals treated with doxorubicin alone were significantly more damaged. Intensive interstitial edema was observed, as well as vacuolization of cardiomyocytes, hypercontraction of sarcomeres, mitochondria of irregular shapes. qRT-PCR results have shown that neither treatment with doxorubicin alone nor the pretreatment with the nanocomposite did cause significant increase in mRNA levels of catalase and superoxide dismutase.

Conclusions: Our results indicate that the fullerenol/iron nanocomposite applied as pretreatment to doxorubicin induces less damage to the hearth tissue in comparison to doxorubicin alone.

Legal entity responsible for the study: Aleksandar Djordjevic

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Disclosure: All authors have declared no conflicts of interest.

1686P Ability of TMPRSS2-ERG (TE) expression to predict taxane benefit depending on prior abiraterone or enzalutamide therapy in castration-resistant prostate cancer

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Background: TMPRSS2-ERG (TE) results in androgen-driven overexpression of ERG, which is involved in resistance to taxanes in preclinical models. In prior work we showed that TE expression in blood correlated with taxanes resistance in metastatic castration-resistant prostate cancer (mCPRC). Here, we studied if the detection of TE in primary tumors predicts taxanes activity in CPRC. We also explored the impact of prior abiraterone or enzalutamide (A/E) in blood TE detection and in TE predictive value.

Methods: mCRPC patients (pts) treated with taxanes in a multicenter biomarker study were included. Formalin-fixed paraffin-embedded (FFPE) tumors and peripheral blood mononuclear cells (PBMCs) fraction were tested for TE presence by RT-qPCR. FFPE were retrospectively obtained. PBMCs were prospectively collected prior to taxane initiation. PSA-PFS was evaluated by Kaplan-Meier analysis using log-rank test. Univariate analysis of TE status (+ vs-) was performed with Cox regression.

Results: 124 pts were included: 111 (89.5%) received docetaxel (Dx), 13 (10.5%) cabazitaxel (Cz) and 27 (21.8%) both. Fifty-seven (45.9%) tumors were *TE*+. Overall, no correlation between tumor *TE* expression and taxane benefit was observed in the whole population, or in the Dx or Cz group separately. However, in Dx-treated pts without prior A/E (N = 80, 72.1%), tumor *TE*+ correlated with lower PSA-PFS (median 8.6 vs 13.6 months; HR 1.7, $p \leq 0.05$). No differences were observed in Dx treated pts with prior A/E (N = 31, 27.9%) according to tumor *TE* expression. In 44 pts, matched tumor and PBMC samples were available. Concordance between tumor an blood was 92.8% and 63.3% for pts with and without prior A/E, respectively. *TE* in blood was + in 1 (7%) pts with prior A/E and in 7 (23.3%) pts without prior A/E. As observed in FFPE samples, in patients without prior A/E to Dx (N = 28; 63.6%), blood *TE*+ correlated with lower PSA response (0% vs 61.9%, $p \leq 0.01$) and reduced median PSA-PFS (3.34 vs 8.2 mM; HR 4.1 $p \leq 0.01$).

Conclusions: The predictive value of *TE* in taxane resistance may be different depending on prior exposure to A/E. This is being tested in a multicenter prospective study.

Legal entity responsible for the study: Hospital Clínic of Barcelona/Institut d'Investigacions Biomèdiques Agust Pi i Sunyer

Funding: None

Disclosure: A. González del Alba: Advisory boards: Sanofi, Janssen, Astellas, Bayer Travel expenses: Astellas, Sanofi, Janssen. All other authors have declared no conflicts of interest.

1688P Identification of patient population with longer survival when treated with S-1 plus cisplatin via predictive enrichment strategy analysis of the FLAGS and DIGEST phase III trial

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Background: The FLAGS trial, a randomized phase III trial, compared S-1, an oral fluoropyrimidine, plus cisplatin (SP) with 5-fluorouracil plus cisplatin (FP) in the first-line treatment for advanced gastric cancer (AGC). The results led to the approval of SP by EMA, and it is now marketed in Europe. The purpose of this analysis was to establish a clinical covariate(s) model using the Predictive Enrichment Strategy Analysis (PESA) identifying patients who benefit from SP.

Methods: PESA is a new robust methodology with guidelines by the United States Food and Drug Administration. Consensus-based 15 clinical covariates were selected for PESA and a large cohort with no missing data (FLAGS trial: 889 patients (pts)) was analyzed. The models generated were cross-validated and the results analyzed were validated in the DIGEST trial, a phase III trial comparing SP to FP in diffuse type advanced gastric cancer. From the DIGEST trial, 333 patients and 14 clinical covariates were used in the analysis.

Results: In FLAGS, ECOG Performance status (PS = 1) was the strongest covariate in the enrichment group showing benefit for SP. In the population with PS = 1, the OS in the SP group was significantly longer than the FP group (Hazard Ratio [HR]=0.798, 95%CI = (0.66-0.96) p = 0.0166). Other covariates with high potential to be associated with SP benefit included: diffuse-type histology, positive peritoneal metastases, and the lack of liver metastases. In DIGEST PS = 1 also showed to be most associated with SP benefit. While there was no strong signal from the variables positive peritoneal metastases, and the lack of liver metastases, there appeared to be a signal from the neutrophil variable. In the DIGEST population of diffuse type, patients with PS = 1 and low baseline neutrophil count may benefit from SP.

Conclusions: Presence of PS = 1 was associated with SP benefit in both the FLAGS and DIGEST trial. Although peritoneal and liver metastases resulted in slightly different signals in the trials, further analyses will be done to look at the impact of low baseline neutrophil count on the benefit of SP for PS = 1 and diffuse type histology patients.

Clinical trial identification: FLAGS trial; ClinicalTrials.gov NCT00400179 First received: June 30, 2005 Last updated: March 28, 2012 Last verified: March 2012 DIGEST trial; ClinicalTrials.gov NCT01285557 First received: January 26, 2011 Last updated: October 19, 2016 Last verified: October 2016.

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1689P HMGA1 is a new biomarker of liposarcoma progression

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Background: Liposarcoma (LPS) is the most common type of soft-tissue sarcoma that includes a heterogeneous class of tumors classified according to histologic appearances, protein expression pattern and molecular genetics. Molecular subtyping is not only important for accurate diagnosis but may be necessary as a basis for the identification of therapeutic targets. Lipoma is characterized by extensive High Mobility Group A1 (HMGA1) protein aberrations suggesting a role of this protein in the mechanisms of liposarcoma progression as well as previously demonstrated in other tumors.

Methods: Cell lines derived from different liposarcoma subtypes and a cohort of 68 patients were used to analyze in vitro and in vivo the role of HMGA1 in liposarcoma progression.

Results: Our data revealed that HMGA1 is highly expressed in liposarcoma cell lines and that is strongly involved in the mechanism of cell proliferation, mobility and invasion of this subtype of tumor. The *in vitro* results were confirmed *in vivo* by the RT-PCR and IHC analyses of 68 specimens of different subtypes of liposarcoma derived from patients surgically treated at Regina Elena National Cancer Institute. The aggressive subtypes de-differentiated and myxoid liposarcoma showed higher HMGA1 levels than well-differentiated liposarcoma. Furthermore, trabectedin, a marine alkaloid isolated from the tunicate *Ecteinascidia turbinata*, down-regulates HMGA1 and E2F1, as well as its downstream targets Vimentin and ZEB1 in sensitive myxoid liposarcoma cells, suggesting a critical role of the transcriptional complex HMGA1/E2F1 in the regulation of the mesenchymal compartment. These data were further confirmed *in vivo* by the IHC analysis of myxoid sarcoma specimens derived from patients that received trabectedin therapy before surgery. On the other hand, trabectedin treatment down-regulates the activity of HER3 receptor that in turn inhibits Nf-kB pathway in sensitive myxoid liposarcoma cells but not in resistant counterpart cells demonstrating that the activation of Nf-kB pathway is involved in the mechanisms of drug resistance.

Conclusions: Overall, our data suggest that HMGA1 may represent a new biomarker of liposarcoma progression and that it could be a new potential therapeutic target for the more aggressive liposarcoma subtypes.

Legal entity responsible for the study: Regina Elena National Cancer Institute

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Disclosure: All authors have declared no conflicts of interest.

1690P hsa_circ_0004870 is related to AR-V7 expression and may confer resistance to enzalutamide in castration-resistant prostate cancer

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Background: Androgen deprivation therapy is the mainstay of prostate cancer treatment, however, resistance inevitably develops, resulting in a more aggressive disease, known as castration-resistant prostate cancer (CRPC). While, enzalutamide provides a substantial survival benefit by targeting the AR, it is not curative and many patients develop resistance to therapy. Although not yet fully understood, resistance can develop through multiple mechanisms, such as AR copy number gain or the generation of splice variants such as AR-V7. circular RNAs (circRNA) are a type of non-coding RNA that have an important function in gene regulation and may play a role in drug resistance, through the regulation of miRNA circRNAs are tissue specific, stable and may represent a novel marker of drug resistance in PCa.

Methods: circRNA profiling was performed on an isogenic PCa cell line model consisting of enzalutamide sensitive and resistant subtypes using a high throughput microarray assay. Subsequently, bioinformatic analyses predicted five miRNA binding sites (miRNA Response Elements) for each circRNA and these were stratified based on known associations with PCa. Targets were validated using qPCR.

Results: circRNAs were more often downregulated in resistant cell lines compared to sensitive lines (588 versus 278). hsa_circ_0004870 was significantly downregulated in enzalutamide resistant cells compared with control. RBM39 was determined as the parental gene, which encodes a member of the U2AF65 family of proteins. Previous studies have shown that, U2AF65 results in the expression of AR-V7, by binding to AR pre-mRNA. Expression of all genes were confirmed within our enzalutamide model.

Conclusions: hsa_circ_0004870 is linked to the generation of AR-V7 and may play a key role in the development of enzalutamide resistance in CRPC via a miRNA mediated mechanism.

Legal entity responsible for the study: Trinity College Dublin

Funding: Irish Cancer Society

Disclosure: All authors have declared no conflicts of interest.

1691P Analysis of DPYD and UGT1A1 genotype in patients with advanced pancreatic cancer treated with modified FOLFIRINOX

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Background: Modified FOLFIRINOX (mFOLFIRINOX) is a standard treatment in advanced pancreatic cancer (aPC). Because of the presence of either loss-of-function mutations in DPYD (c.1679T>G, IVS14 + 1G>A, c.2194G>A, c.2846A>T) or UGT1A1*28 variant associated with reduced UGT1A1 expression, deficiency of DPD and UGT may result in drug accumulation and severe toxicities caused by fluoropyrimidines and irinotecan, respectively.

Methods: The present study analyzes the association between DPYD and UGT variants and adverse drug reactions (ADRs) in aPC patients (pts) treated with mFOLFIRINOX. Blood samples were collected from 104 pts, and analyses of DPYD c.1679T>G, IVS14 + 1G>A, c.2194G>A, c.2846A>T and UGT1A1*28 were performed by automatic sequencing. Statistical analysis was performed by chi-square, Mann-Whitney and Spearman's rho tests on SPSS v.23s.

Results: None of the pts was carrier of the c.1679G and c.2846T alleles. Only one IVS14 + 1GA was found and 8 pts had c.2194GA genotype. ADRs grade (G) ≥3 were neutropenia (42.3%), diarrhea (7.7%) and stomatitis (7.7%). The statistical analysis of the IVS14 + 1GA has not been performed due to the extremely low frequency of the mutant allele (0.96%), however IVS14 + 1GA patient experienced G4 hematological and gastrointestinal ADRs after the first cycle. We observed a trend toward significant association between c.2194GA genotype and the risk of thrombocytopenia ($p = 0.080$) and hand-foot syndrome (HFS) ($p = 0.096$). The UGT1A1*28 allele was found in 56 (54.4%) pts (*1/*28, n = 38; *28/*28, n = 18) and it was correlated with the risk of developing thrombocytopenia ($p = 0.006$) and neutropenia ($p = 0.044$). Moreover, this risk increased as the number of *28 alleles increased (*28/*28 > *1/*28 > *1/*1, $p = 0.003$). No significant correlation with diarrhea was found.

Conclusions: Our data confirm that DPYD IVS14 + 1A is associated with life-threatening toxicities and that the c.2194A allele could be possibly associated with thrombocytopenia and HFS, but validation in larger cohorts is needed. UGT1A1*28 allele is associated with a higher risk of G3/4 thrombocytopenia and neutropenia, and should be implemented in routine practice to personalize treatment in aPC.

Legal entity responsible for the study: University of Pisa

Funding: Institutional fundings

Disclosure: All authors have declared no conflicts of interest.

1692P Clinical significance of the expression of membrane receptors of the alternative nuclear factor-kappaB pathway in non-small cell lung cancer

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Background: During the last decade, the alternative pathway of Nuclear Factor-kappaB (NF-κB) has gained importance due to its implication in cancer initiation and development where it has been shown to be deregulated. It is mainly activated thgough the membrane receptors Lymphotoxin β Receptor (LTβR), CD40, B-cell activating factor receptor (BAFFR) and Receptor Activator of NF-κB (RANK), having an important role in immune response and multiple cancer cell functions.

Methods: Immunohistochemical analysis of the expression of these 4 receptors was performed on 130 tumour and adjacent non neoplastic formalin fixed and paraffin embedded tissue samples from patients with non-small cell lung cancer (NSCLC).

Results: CD40 and BAFFR expression was higher in neoplastic compared to adjacent non-neoplastic tissue ($P = 0.006$ and 0.001, respectively) while no such differences were observed for RANK and LTβR. Moreover, CD40 levels in tumour infiltrating lymphocytes (TILs) correlated with development of metastases in adrenals ($P = 0.003$), liver ($P < 0.001$) and in brain ($P = 0.048$), while CD40 levels in stromal cells correlated with liver metastasis ($P = 0.013$). Cytoplasmic BAFFR expression in cancer cells was associated with T status while BAFFR levels in stromal cells were related to 2-year survival ($P = 0.034$). Cytoplasmic RANK expression was associated with membrane levels in cancer cells ($P < 0.001$) but was independent of any clinicopathological characteristics. Finally, nuclear detection of LTβR was related to histological subtypes with squamous cell carcinoma having higher levels cmpared to adenocarcinomas ($P = 0.026$).

Conclusions: Protein levels of CD40 and BAFFR are altered in NSCLC in agreement with a deregulation of the alternative NF-κB pathway previously shown by our team. CD40, BAFFR and LTβR tissue protein levels appear to constitue biomarkers for specific clinicopathologcal parameters including survival, stage and histological subtype.

Legal entity responsible for the study: Haralabos P Kalofonos.

Funding: Hellenic Society of Medical Oncology (HeSMO).

Disclosure: T. Makatsoris: Travel expenses from Pfizer, Roche and Astellas. Advisory fees from Roche and Boeringer. Honoraria from Roche, Sanofi, Merck and Amgen. H. Kalofonos: Consulting/advisory role: Roche, Novartis, MSD, Genesis, Pfizer, Lilly, Leo, Amgen, Janssen, Merck, Merck-Serono.Research funding Roche Pfizer, Novartis, Amgen, Bayer, Genesis Lilly, MSD, Janssen, Merck-Serono. Travel expenses: Roche, Novartis, Enorasis, Pfizer. All other authors have declared no conflicts of interest.

1693P Development of TP53 signature diagnostic system using multiplex RT-PCR and observational study to confirm the prognostic value of TP53 signature in breast cancer

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Background: The structural mutation status of *TP53* gene is well known independent prognostic factor of breast cancer. We have reported that status of the *TP53* mutation is predictable by expression profile of 33 genes ('*TP53* signature') in breast cancer. The *TP53* signature was reported to be one of the best predictors of prognosis and therapeutic effect by meta-analysis (BMC Cancer, 2015). The aim of this study is to develop a simple diagnostic system for *TP53* signature using multiplex RT–PCR and confirm the prognostic value of *TP53* signature.

Methods: We made the multiplex RT-PCR system consists of 26 genes, 23 genes from the *TP53* predictive genes and 3 internal control genes. *TP53* signature status was determined by the ratio of the sum of expression levels of 16 genes that were upregulated in tumors with *TP53* mutation to the sum of expression values of 7 genes downregulated in tumors with *TP53* mutation. Cutoff value was set at 1.11 to maximize the sensitivity to detect the *TP53* mutant signature. Using a 217 breast cancer case cohort, which was prospectively collected from 2007 to 2010, the relationship between the *TP53* signature status and clinicopathological features and *TP53* structural mutations were analyzed. And we validated the prognostic value of *TP53* signature in 191 stage I-II patients.

Results: Of 217 patients, 102 patients were assigned to the *TP53* mutant signature. *TP53* structural mutation was observed in 35.1% of patients with *TP53* mutant signature and 6.3% of patients with *TP53* wild-type signature. In 191 stage I-II patients, RFS of the patients with *TP53* mutant signature showed significantly shorter than the patients with wild-type signature. Similar result was observed in 164 ER positive patients. In both univariate and multivariate analyses, *TP53* signature status showed independent and better correlation to RFS than tumor size, LN status, stage, ER status and *TP53* structural mutation status in stage I-II patients.

Conclusions: We developed the diagnostic system to determine *TP53* signature status using multiplex RT-PCR. The *TP53* status diagnosed by this system could be one of the prognostic biomarker of breast cancer.

Clinical trial identification: UMIN000005172.

Legal entity responsible for the study: Ethics Committee at the Tohoku University Hospital.

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Disclosure: All authors have declared no conflicts of interest.

1694P Expression of estrogen receptors and beta-III tubulin in non-small cell lung cancer tissue

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Background: Estrogen receptors beta (ERβ) are highly expressed in different normal and neoplastic tissues that, until recently, has been considered to be ER-negative based on ERα expression evaluation. Among the genes, regulated via estrogen signaling there is one, coding microtubule protein beta-III tubulin (TUBB3). TUBB3 expression is found in many solid tumors and is linked to poor prognosis and resistance to taxanes. Since it is little known about mechanisms behind TUBB3 expression in non-small cell lung cancer (NSCLC), we decided to find out if there is a correlation between ER and TUBB3 expression in this type of cancer.

Methods: 104 surgical samples of NSCLC were converted to single-cell suspension, stained with primary anti-ERα (abSP-1), anti-ERβ (ab14C8), anti-TUBB3 (ab7751) antibodies and secondary fluorescent antibodies. Immunofluorescent estimation was performed using flow cytometry. Expression level was determined as the ratio (%) of specifically fluorescent cells to the number of cells stained with secondary antibodies. Spearman rank correlation was used to test the association between variables.

Results: Both ER were revealed in all NSCLC specimens. Mean expression level of ERβ was significantly higher compared with ERα (46,6 ± 17,0% vs 23,2 ± 14,2%, respectively). Mean TUBB3 expression level was 43,1±15,7%. In all the tumors investigated only weak correlation observed between and ER status and TUBB3 expression level ($rs = 0,3$ and $rs = 0,4$ for ERα and ERβ, respectively). In the group of squamous cell cancer specimens ($n = 68$) the association was strong ($rs = 0,5$ and $rs = 0,5$ for ERα and ERβ, respectively). In the group of adenocarcinoma specimens ($n = 36$) the correlation between ERα and TUBB3 was very weak ($rs = 0,3$) and there was no correlation between ERβ and TUBB3.

Conclusions: 1. Strong correlation between TUBB3 and ER expression was found only in squamous cell cancer tissue. 2. The dominant type of estrogen receptors is ERβ. 3. In clinical terms high ERβ expression means that in case of resistance to standart platinum/taxane duplets, patients with high tumor ERβ expression may benefit from antiestrogen therapy. Supported by RFBR grants (№№15-04-06991-a, 16-34-01049-mol-a) and grant of the President of RF MK-7709.2016.7.

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Disclosure: All authors have declared no conflicts of interest.

1695P Deciphering the antitumor efficacy and mechanistic delineation of epigenetic inhibitors in AML using patient tumor derived ex vivo phenotypic assay based platform

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Background: Epigenetic inhibitors have demonstrated tumor efficacy by modulating genes involved in growth, proliferation, and invasiveness in hematological malignancies like AML. Preclinical evidences suggest therapeutic benefit by combining epigenetic drugs along with other therapeutics like JAK2 inhibitors. However, there is a huge unmet need to understand the disparities in response at the individual patient level.

Methods: We developed a novel functional assay based platform called CANscript™ to predict the efficacy of anticancer drugs in clinic, which mimics patient tumor microenvironment (Majumder B et al., *Nature Communications*, 2015). Utilizing samples from AML patients we interrogated response to HDAC and DNA MTase inhibitors by assessing tumor viability, proliferation, morphology, and death in this platform. To elucidate the mechanisms of response, we delineated the pharmacodynamic and pathway modulation by immunohistochemistry and mRNA microarray.

Results: Thirty-two AML patients samples were analyzed in this platform. HDAC and DNA MTase blockade resulted antitumor response, which was demonstrated by differential and quantitatively distinct patterns of target engagement. mRNAs and pathway specific protein expression profiling is suggestive of JAK2 pathway deregulation in many of the non-responders. Treatment with JAK2 inhibitor in this cohort led to efficacy in 40% of these non-responders, suggesting the critical role of this pathway. Interestingly, unique JAK2 signatures associated with single agent vs. combination therapy was observed (10%), hinting at functionally distinct mechanisms of antitumor effects at individualized levels.

Conclusions: These findings demonstrate the utility of this ex vivo platform to predict therapeutic response of epigenetic modulators at the individual patient tumor. It also highlights that, within a contextually heterogeneous framework, distinct mechanisms orchestrate response to HDAC and DNA MTase inhibitors as a single agent or in combination with JAK2 inhibitors. Insights gained from these findings can re-shape our strategic thinking of drug selection for the treatment of AML.

Legal entity responsible for the study: Mitra RxDx

Funding: Mitra RxDx

Disclosure: G. Babu: Independent consultant and full time employee of Kidwai Memorial Institute of Oncology, scientific and clinical advisory board of Mitra Biotech and equity in this organization. All other authors have declared no conflicts of interest.

1696P Proteomics of triple negative breast cancer developing metastases to central nervous system

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Background: Breast cancer (BC) is the most frequent tumor in woman, representing 20-30% of all malignancies and continues being the first reason of death for cancer in European women. Triple negative (TN) BC present minor survival rates than other BC subtypes. Key reasons for that is the absence of predictive markers of response to current therapy and the absence of targeted therapies. This study aims to identify proteins with predictive value of central Nervous System (CNS) metastases and therapeutic target candidates.

Methods: This is a case-control retrospective study comparing patients (pts) with metastases to CNS vs pts without them after adjuvant treatment. Sample selection included 50 samples. Formalin-fixed, paraffin-embedded samples were retrieved from Hospital 12 de Octubre Biobank. Proteins were quantified by parallel reaction monitoring.

Results: The average age was 55 years (range 25-85). Forty-seven pts (88.67%) had ductal histology and presented high grade tumors (40 pts; 75.47%). Eight women in the case group presented as first distant recurrence CNS (34.80%), local recurrence (3pts, 13.04%), lung (2pt; 8.7%), bone (1pt; 4.34%) and other locations (7pts; 30.38%). In the control group, first distant recurrence occurred locally (6pts; 46.1%), bone (2pts; 15.4%), lung (1pt; 7.7%) and other sites (4pts; 23.1%). Protein expression data was successfully obtained from 50 samples. ISG15 ubiquitin-like modifier, (P05161) was overexpressed in triple negative breast cancer tumors that develop metastases to CNS ($p = 0.036$) compared to tumors that do not develop these CNS metastases.

Conclusions: TN tumors frequently metastasize to visceral organs, particularly lungs and brain, and are less likely to metastasize to bone. The interferon-stimulated gene 15 ubiquitin-like modifier (ISG15) encodes an IFN-inducible, ubiquitin-like protein. The ISG15 protein is involved in numerous cellular functions, including interferon-induced immune responses and the regulation of cellular protein turnover. Therefore, ISG15 may represent a novel breast tumor marker helpful in selecting pts who will develop CNS metastases. It also should be explored as a therapeutic target in this clinical context.

Legal entity responsible for the study: Biomedica Molecular Medicine SL.

Funding: None.

Disclosure: L. Trilla-Fuertes: Employee of Biomedica Molecular Medicine SL. A. Gámez, J.A. Fresno: Shareholders in Biomedica Molecular Medicine SL. All other authors have declared no conflicts of interest.

1697P Assessing functional Androgen Receptor (AR) pathway activity using a computational model

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Background: Cellular signal transduction research identified 10-15 signaling pathways responsible for driving tumor growth. Defining pathway activity in tumor tissue is necessary to optimize targeted therapy choice. Verhaegh *et al* (Cancer Research 2014) used a Bayesian network approach to model transcriptional programs of signaling pathways. These pathway models use mRNA expression levels of validated direct pathway target genes to infer a probability of pathway activity in individual patient samples. Here, initial results of the AR model are presented.

Methods: 28 bona fide AR target genes were selected and a Bayesian network model for the AR pathway was built and calibrated. The model uses target genes mRNA levels (Affymetrix HG-U133Plus2.0 array) as input to infer probability of AR pathway activity. Evaluation was done using multiple public datasets from clinical studies. The model was also adapted for qPCR data as input, using a subset of most informative target genes.

Results: Biological validation on androgen stimulated LNCaP cultures showed expected AR activity (GSE7868), which was inhibited by the anti-androgen bicalutamide (GSE7708). In cell line xenograft models (GSE21887, GSE33316, GSE966), AR was active in the presence of androgen and inactive in castrated mice. In prostate hyperplasia and 90% of primary prostate cancer (PCa) samples (GSE17951, GSE28403, GSE32982, GSE3325, GSE45016) AR was active; in contrast, AR was inactive in 30-50% of castration resistant or metastatic samples. AR was active in primary PCa samples, but not in samples taken 3 days after surgical castration (GSE32982). In other cancer types AR was mostly inactive, except for a subset of Her2 subtype Breast Cancer (BCa), Luminal BCa (EM-TAB-365, GSE12276, GSE17097, GSE21653), and meningioma samples (GSE16581, GSE9438). Translation to qPCR-RNA measurement as input was successful, underscoring the portability of our approach to other measurement platforms

Conclusions: Our biologically validated computational AR model enables assessing functional AR pathway activity in individual patient tissue samples, based on mRNA microarray or qPCR input from respectively FF or FFPE material. Other pathway models and clinical validation studies are in progress.

Legal entity responsible for the study: Philips Research

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1698P Evaluation of deamination bias from formalin-fixed tissues of small cell lung cancer with a dual strand targeted amplicon sequence

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Background: Precision medicine is dependent on identifying actionable mutations in tumors. Accurate detection of mutations is often problematic in formalin-fixed paraffin-embedded (FFPE) tissues, as it causes DNA damage such as fragmentation and cytosine deamination. These Sequence artifacts can be difficult to distinguish from true mutations, and are an increasing interpretive issue. Understanding of the characteristics of these sequence artifacts in FFPE tissues is critical to improve the accurate detection of actionable mutations.

Methods: We reviewed the clinical courses of 156 small cell lung cancer (SCLC) patients who had undergone surgery at 17 institutions in Japan between January 2003

and January 2013. In these patients, we obtained the FFPE tissues of 79 cases which were histopathologically confirmed as SCLC and fitted for sequencing analysis with suitable DNA quality. Targeted amplicon sequence was conducted with MiSeq and TruSight panel (Illumina) which is a dual stranded amplicon kit for detecting cytosine deamination. We evaluated the characteristics of deamination bias and the relations with institutions and age of the tissue block.

Results: We could evaluate sequence of 73 samples data from 14 institutions. Target region of the sequencing was 26 genes, total 14686 bp. The total discordant single nucleotide variant (SNV) between forward and reverse strand were 690 cases, 16.4 cases per sample. The highest number of discordant SNV was 132 per sample. The most part of discordant SNV was the deamination change (C>T/G>A), 589 (85.4%) of 690 cases. The highest discordant SNV frequency was 0.25 with read depth 1876 in deamination change pattern, and 0.10 with read depth 4196 in the others. The frequency of the deamination change was different by institutions more than age of the tissue block.

Conclusions: Cytosine deamination from formalin fixation can be a major issue in diagnostic test of genome DNA for cancer samples. Procedures that assess, minimize or remove formalin-induced influences is important in the interpretation of genomic DNA analysis leading to better practice.

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Disclosure: All authors have declared no conflicts of interest.

1699P Functional genomic mRNA (FGmRNA) profiling of > 18,000 tumor samples identifies potential new indications for antibody-drug conjugates (ADCs) in a broad range of tumor types

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Background: ADCs, consisting of an antibody designed against a specific antigen at the cell membrane linked with a cytotoxic agent, are an emerging class of therapeutics. Since ADC targets do not have to be drivers of tumor growth, ADCs are potentially relevant for a wide range of tumor types. Therefore, we aimed to define the landscape of ADC target expression in a broad range of tumor types.

Methods: PubMed and ClinicalTrials.gov were searched for ADCs that are or were evaluated in clinical cancer trials. Gene expression profiles of 18,055 patient derived tumor samples representing 60 tumor (sub)types and $\geq$ 3,520 samples representing 22 healthy tissue types were collected from the public domain. Next, we applied FGmRNA-profiling (Fehrmann *et al.* Nat Genet 2015;47:115-25) to predict per tumor type the overexpression rate at the protein level of ADC targets with healthy tissue samples as reference.

Results: We identified 87 ADCs directed against 59 unique targets. 17 ADC targets showed predicted overexpression of $\geq$ 75% of samples in at least 1 tumor (sub)type, 38 $\geq$ 50% and 56 $\geq$ 25%. A predicted overexpression rate of $\geq$ 10% of samples for multiple ADC targets was observed for high incidence tumors like breast cancer ($n = 31$ with $n = 23$ in triple negative breast cancer), colorectal cancer ($n = 18$), lung adenocarcinoma ($n = 18$), squamous cell lung cancer ($n = 16$) and prostate cancer ($n = 5$). In rare tumor types we identified targets showing high predicted overexpression, for example in uveal melanomas we found 95% predicted overexpression for c-MET.

Conclusions: This study provides a data driven prioritisation of available ADCs for clinical evaluation in 60 tumor (sub)types. This comprehensive ADC target landscape can support clinicians and drug developers in trial design.

Legal entity responsible for the study: UMCG

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TUMOUR BIOLOGY AND PATHOLOGY

1700O Genomic profiling of 114,200 advanced cancers identifies recurrent kinase domain duplications (KDD) and oncogenic rearrangements (RE) across diverse tumor types

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Background: Kinase fusions (KFN) are well recognized as targetable drivers in some cancers, and KFN common in one disease can be found in unrelated histologies, as for *BRAF*. Recently, oncogenic KDD in *BRAF* and *EGFR* were reported, along with responses to tyrosine kinase inhibitors (TKI). We assessed the frequency of KDD and KFN across 114,200 advanced cancers to reveal the landscape of oncogenic KFN and non-canonical rearrangements (KRE) in a wide variety of subtypes.

Methods: CGP was performed on DNA and/or RNA from 114,200 solid tumors or heme malignancy samples for 184-406 cancer-related genes and select introns from 14-28 genes commonly rearranged in cancer. RNA sequencing for 265 genes was available for some cases. Selected genomic events were confirmed by manual inspection.

Results: KDD were observed in 598 cases (0.62%): *BRAF* (127), *EGFR* (115), *FGFR3* (94), *FGFR1* (40), *RET* (37), *ERBB2* (35), *PDGFRA* (35), *FGFR2* (28), *MET* (19), *ROS1* (14), *ALK* (13), *KIT* (8), *NTRK1* (8), *FLT3* (6), *FGFR4* (5), *ERBB4* (4), *PDGFRB* (3), *NTRK2* (2). KDD were seen in 2.7% of brain tumors, most often *EGFR* (66), *BRAF* (52), *PDGFRA* (13), and *FGFR3* (26). In extracranial tumors, KDD were common for *RET* (13-16% of breast, lung, and thyroid KDD+ cases), *MET* (15-20% of uterine and brain KDD+ cases), and *ALK* (54% of lung KDD+ cases). KDD possibly related to TKI resistance were seen in *BRAF* V600E-positive melanoma and *ALK*-related NSCLC. Table 1 summarizes KFE and KFN for *ALK*, *FGFR2/3*, *RET*, and *ROS1*; 48-57 tumor types are affected per gene. KFN partner varied by tumor site; for *ROS1*, *GOPC* KFN predominate in gliomas and CRC, *TFG* KFN in sarcomas, and *CD74* and *EZR* in NSCLC.

Conclusions: KDD are enriched in brain tumors. Diverse KDD are found extracranially and may underlie acquired resistance. Index cases with clinical responses to matched TKIs suggest KDD, KFN and KRE can be targeted therapeutically in many histological subtypes. Recurrent KFN are found widely in cancer, with gene partner varying by subtype.

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1701O Comprehensive Genomic Profiling (CGP) of Thymic Gland Carcinomas

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Background: Thymic gland carcinomas include a variety of histologic subtypes with variable clinical aggressiveness and response to local and systemic therapies. We queried whether CGP could refine tumor subtypes and uncover new targeted and immunotherapy options for patients with relapsed and metastatic disease (mTC).

Methods: FFPE sections of 174 consecutive cases of mTC was sequenced using hybridization-captured, adaptor ligation-based libraries to a mean coverage depth of > 500X for up to 315 cancer-related genes plus 37 introns from 28 genes frequently rearranged in cancer. Total mutational burden (TMB) was determined on 1.1 Mb. Clinically relevant genomic alterations (CRGA) were defined as GA linked to drugs on the market or under evaluation in mechanism driven clinical trials.

Results: All mTC were clinically advanced and included 4% adenocarcinomas (TAC), 3% basaloid (TBC), 3% lymphoepitheliomatous (TLEC), 17% neuroendocrine

Table: 1700O

		ALK		FGFR2		FGFR3		RET		ROS1	
	All Samples	FN	RE	FN	RE	FN	RE	FN	RE	FN	RE
NSCLC	20868	590	76	10	5	32	5	240	30	189	7
Brain	6317	3	–	7	2	82	5	3	1	24	6
Pancreatobiliary	7934	8	1	178	50	7	2	7	5	2	5
Bladder	1458	–	–	1	–	39	10	–	–	–	2
Thyroid	972	5	–	2	–	–	–	38	2	1	–
All Other	76651	132	27	122	65	89	14	71	34	38	53

Table: 1701O

	TAC	TBC	TLEC	TNEC	TNOS	TSCC	TSRC
Patients	7	5	5	30	54	69	4
Median Age (y)	48	58	50	48	57	57	61
Gender	43% F	60% F	20% F	37% F	24% F	34% F	50%F
GA/tumor	4.0	2.8	1.0	3.3	4.1	4.1	4.8
CRGA	0.9	0.3	0	0.9	0.8	1.0	1.0
Significant GA	*PDGFRA FGFR3 KIT MET PTCH1*	*CDKN2A FBXW7*	*CDKN2A MEN1*	*KIT BRCA2 IDH1 ERBB2 ERBB3*	*KIT PTEN PIK3CA*	*KIT FGFR3 PIK3CA*	*ERBB2 IDH1 KIT*
TMB >10 mut/Mb	14%	0%	0%	3%	5%	9%	0%
TMB >20 mut/Mb	0%	0%	0%	3%	5%	9%	0%

(TNEC), 31% non-NE undifferentiated (TNOS), 40% squamous and 2% sarcomatoid (TSRC) carcinomas (Table). mTC were twice as common in men than women, had a peak incidence in late middle age, and featured an average of 4 GA/case and 0.9 CRGA/case. The most common molecular targets were *KIT* and *PIK3CA*. Other targets were *PDGFRA*, *FGFR3*, *PTCH1*, *FBXW7*, *BRCA2*, *IDH1*, *ERBB2* and *ERBB3*. The more frequent subtypes (TNEC, TSCC and TNOS) tended to have more GA, with *KIT* targets in ~ 10% of cases. Low TMB in mTC was common; only 6% of cases had >10 mut/Mb and 3% had >20 mut/Mb. Examples of mTC with responses to targeted therapies will be presented.

Conclusions: mTC histologic subtypes have varying GA and TMB status. The more common TSCC, TNEC and TNOS feature more GA, and when combined with TAC have more CRGA including KIT mutations and higher TMB. CGP shows promise to guide both targeted and immunotherapy selection for patients with this rare malignancy.

Legal entity responsible for the study: Jeffrey S Ross

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1702O Clinical implications of genomic variants identified in over 30,000 advanced-stage cancer patients by next-generation sequencing of circulating tumor DNA

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Background: Next-generation sequencing (NGS) of circulating tumor DNA (ctDNA) enables non-invasive profiling of solid tumor cancers. Over the past few years, research and clinical practice guidelines have highlighted a role for liquid biopsy in patient care; however, few large datasets on clinical use have been published.

Methods: Somatic genomic profiles of 35,492 plasma samples from 30,024 advanced cancer patients were determined by a ctDNA NGS test targeting up to 73 genes (Guardant360®). Accuracy of ctDNA-detected driver alterations (PPV) was assessed by comparing to available matched tissue tests for 646 patients (lung, colon, and other cancer types). A pooled response rate analysis was performed across published/in press datasets presenting response data to alterations detected by Guardant360®.

Results: The full cohort consisted of non-small cell lung cancer (NSCLC) (39%), breast (16%), colorectal (CRC) (10%) and multiple other solid cancer types (35%), with ctDNA alterations detected in 88%, 86%, 88%, and 82%, respectively (86% overall). 19% of patients had 1 or more ctDNA alterations associated with an FDA-approved therapy. Resistance variants were identified in 18% of NSCLC, breast, CRC, prostate, melanoma and GIST patients. PPV ranged from 92-100% for EGFR L858R/E19del/E20ins (98%), ALK/RET/ROS1 fusions (92%), BRAF V600E (95%), KRAS G12/G13/Q61 (94%), and MET E14 skipping mutations (100%). Pooled response rate to 1st line EGFR TKIs (n = 43 NSCLC): 86% [95% CI: 71-94%]; to osimertinib (n = 19 NSCLC): 94% [72-99%]; to rociletinib (n = 63 NSCLC): 54% [41-67%]; to crizotinib (n = 11 NSCLC): 82% [48-97%]; to anti-HER2 agents (n = 7 breast): 86% [49-97%]; (n = 5 gastric): 80% [37-96%].

Conclusions: Use of liquid biopsies is increasing in clinical care, providing an option of obtaining genomic information non-invasively. This dataset, derived from liquid biopsy use in clinical practice, highlights the clinical impact of identifying alterations that are targetable by drugs with regulatory approval, including emergent resistance alterations.

Legal entity responsible for the study: Guardant Health, Inc.

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1703PD Landscape of DNA damage response (DDR) genes alterations in the prospective MOSCATO and MATCH R trials

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Background: DDR deficiency is a hallmark of cancer. We aimed at describing in 2 prospective trials run at Gustave Roussy Cancer Campus the molecular and clinical characteristics of patients (pts) harboring DDR gene alterations with special focus on mismatch repair (MMR).

Methods: Pts with metastatic solid tumors enrolled in MOSCATO (NCT01566019) and MATCHR (NCT02517892) trials had on-purpose tumor biopsy; molecular profiling was performed using Targeted Next Generation Sequencing (TGS) and Comparative Genomic Hybridization array (CGHa), or Whole Exome Sequencing (WES). Alterations in 46 genes involved in DNA repair were searched. After review by molecular geneticist, pathogenic variants (PV) were defined as variants causing protein truncation (frameshift indels, nonsense or splice site variants) or known to be deleterious missense variants according to databases such as LOVD, BRCAshare and OncoKB. Variants without deleterious prediction were excluded.

Results: Molecular data of 1092 pts of various histologies enrolled between Dec. 2011 and Oct. 2016 was used. Analysis of TGS (N = 1090), CGHa (N = 838) and WES (N = 304) data allowed identifying 156 alterations in 107 pts (9.8%) and 30 DDR genes: 60 PV, 86 variants of unknown pathogenicity (VUP) and 10 focal deletions (CGHa). Most frequent altered pathways were homologous recombination (47 PV, including 30 BRCA1/2 PV and 7 ATM PV in 13 primary sites) and MMR. The 27 pts with 35 MMR and POLE alterations (12 PV, 20 VUP and 3 deletions) had 11 different primary types including most frequently colorectal, genito-urinary and breast. Only one pt was previously known to have Lynch syndrome. Missense PV occurred most frequently in POLE, MLH1, MSH2, PMS1 (2 each), as well as, MSH3 and MLH3 (1 each); 14/27 pts received immunotherapy (IO). Median PFS was 6.5 months with IO and 6.2 months with conventional therapy. Correlation of MMR aberrations with immune infiltrates and outcome (response, PFS and OS) on IO will be presented at the congress time.

Conclusions: DDR genes alterations occur regularly in solid tumors. Systematic analysis of DDR alterations could allow customizing treatment of pts that specifically benefit from IO or DNA repair inhibitors through synthetic lethality.

Clinical trial identification: NCT01566019 and NCT02517892

Legal entity responsible for the study: Gustave Roussy Cancer Campus

Funding: Gustave Roussy Cancer Campus.

Disclosure: All authors have declared no conflicts of interest.

1704PD Tumor microenvironment biomarkers as therapeutic strategies for TNBC

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Background: Patients with triple negative breast cancer (TNBC) comprise a heterogeneous and poor-prognosis subgroup. Biomarkers for targeted therapy development remains a challenge. Progression of TNBC is associated with extracellular matrix (ECM) remodeling and reactivation of the paracrine Hedgehog (Hh) pathway, highlighting the relevance of tumor microenvironment (TME) in tumorigenesis. We investigated whether TME biomarkers could determine clinical response in TNBC patients treated with the Hh pathway inhibitor sonidegib in combination with docetaxel.

Methods: Patients enrolled in GEICAM/2012-12 (EDALINE) trial were included (n = 12). To evaluate Hh pathway activation, the expression of SHH and GLI1 was centrally examined by immunohistochemistry in pre-treatment primary tumors. A Hh Pathway Activation Signature (HPAS) was defined when SHH expression in epithelium and GLI1 in stroma were high (> median). Biomarkers involved in formation and degradation of ECM (C1M, C3M, C4M, C6M, pro-C3, pro-C6, CRPM, Loxl-2 and VCANM) were evaluated by ELISA (Protein Fingerprint^{TM}) in sequential plasma samples. ECM signature (ECMS) was defined when C4M and VCANM were high at baseline (> median).

Results: Related to Hh pathway activation, only 10 tumors had IHC results. Three patients had high HPAS, 2 of them experienced a clinical benefit, 1 complete response (CR) and 1 stable disease (SD) lasting 7.3 and 5.5 months, respectively. All patients with low HPAS expression progressed. An additional patient had clinical benefit but the status of Hh pathway activation was unknown. For ECM biomarkers, a maintained reduction was observed in the expression along treatment (C2D1-0.5h, C2D2-25h and C4D1) vs baseline for pro-C3 (12.8, 10.2 and 9.4 vs 16.6, $p = 0.05$, $p = 0.03$, $p = 0.25$, respectively), and pro-C6 (9.2, 7.5 and 8 vs 9.95, $p = 0.13$, $p < 0.01$, $p = 0.03$, respectively). Interestingly, patients with high ECMS had better Progression Free Survival ($p = 0.02$). Moreover, 4 patients out of 12 had high ECMS, 3 of them experienced a clinical response, 1 CR and 2 SD. All patients with low ECMS progressed.

Conclusions: Hh pathway activation and ECM remodeling might be associated with improved benefit to sonidegib in combination with docetaxel in TNBC metastatic patients.

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Legal entity responsible for the study: GEICAM Spanish Breast Group.

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1705PD Detection of therapeutic targets in carcinomas of unknown primary

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Background: Current cancer treatment paradigms are based on features of the primary tumour and extent of disease. Carcinoma of unknown primary (CUP) is a histologically confirmed metastatic cancer in the absence of an identifiable primary tumour. As such it is difficult to determine the optimal treatment strategy and 5-year survival rates are less than 20%. This poor survival rate is due to both the unclassifiable metastatic malignancy and the use of empirical broad-spectrum chemotherapy. A shift towards personalising cancer management based on mutation profiling has been explored in many cancer types including CUP. Small studies have reported durable treatment responses in CUP patients receiving targeted therapies, specifically when EGFR and KIT variants are detected. The present study has explored whether biologically important oncogenic driver mutations and potentially actionable targets are present in CUP that have potential to better inform treatment decisions.

Methods: CUP cases (n = 32) diagnosed on histopathology criteria were selected for study. Sections were cut from paraffin blocks of formalin-fixed tissue and DNA isolated. Extracted DNA was amplified with the Ion AmpliSeq Cancer Hotspot panel and Oncomine Focus panel for the identification of biologically relevant and actionable mutations, respectively. Amplified DNA was sequenced using the Ion Torrent platform and data was processed using a stringent variant filtration pipeline.

Results: Biologically relevant or therapeutically druggable variants were detected in 88% (n = 28) of cases. The most common variants were in *TP53* (47%), *KRAS* (19%), *MYC* (6%), *BRAF* (6%) and *CDKN2A* (6%). There were potentially actionable targets in 14/32 (44%) cases, with the most common druggable variants being in the *KRAS* gene (exon 1) (6 cases) and *MYC* gene amplifications (2 cases).

Conclusions: This retrospective study successfully identified biologically relevant variants in 88% of CUP cases. 50% of these variants were potentially actionable with drugs currently approved for use in known primary cancer types or undergoing clinical trials. This would give a novel treatment option to patients with a currently incurable disease with poor survival. The data therefore supports the use of NGS at diagnosis to give biological insight into the drivers leading to the malignancy, and to allow consideration of novel targeted treatment options.

Legal entity responsible for the study: Translational Cancer Pathology Laboratory

Funding: PathWest

Disclosure: All authors have declared no conflicts of interest.

1706PD Analysis of stroma and immune-related gene expression patterns during breast cancer (BC) progression

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Background: Characterization of the immune phenotype of tumors during progression could aid in developing patient-tailored therapy strategies. Here, we sought to identify differences in immune markers comparing paired tumors from primary and metastatic sites from the GEICAM/2009-03 (ConvertHER) study.

Methods: Matched primary and metastases were analyzed by immunohistochemistry as described by Herbst et al., 2014 for PDL1 expression. The nanostring gene expression platform was used to profile and identify differences in the expression of 805 immune-related genes. Significant features (p-value <0.05) were assessed for functional enrichment of KEGG pathways and GO terms.

Results: Out of 44 pairs analyzed for PDL1, 29 (65%) were ER+/HER2-, 3 (7%) ER-/HER2+, 6 (14%) ER+/HER2+ and 6 (14%) ER-/HER2- (TN). PDL1 expression (^{3}1%) was observed in the immune cell (IC) compartment in 11 (19%) ER+/HER2-, 4 (33%) ER+/HER2+, 2 (33%) ER-/HER2+ and 11 (92%) TN samples. No significant differences were observed between primary and metastases. Out of 60 pairs analyzed by nanostring, the most, (40; 67%) were ER+/HER2-, 5 (8%) ER-/HER2+, 7 (12%) ER+/HER2+ and 8 (13%) TN. In the global population, we found that 102 genes were differentially expressed (fold-change >2) between primaries and metastasis. For the ER+/HER2- subgroup, expression of 98 genes significantly differs in metastasis compare to primaries. No clear changes in pre-specified immune signatures were observed, probably due to the high tumor heterogeneity, different treatments and small sample size. Interestingly, analyses of pre-specified gene signatures suggest that metastases have decreased Notch pathway, innate inflammation and TGFb-activated fibroblasts signatures. Moreover, GO-enriched signature analyses suggest that B cell differentiation and type 1 IFN pathway are also reduced in metastases both in the global population and in ER+/HER2- tumors, thus suggesting a decreased immune defense during progression.

Conclusions: Our analysis failed to identify novel immune biomarkers of BC metastases. However, these data pointed out that tumors could relax the immune system response during progression.

Clinical trial identification: NCT01377363.

Legal entity responsible for the study: GEICAM Spanish Breast Group.

Funding: Genentech Inc.

Disclosure: L. Molinero, H. Koeppen: Employee of Genentech. All authors have declared no conflicts of interest.

1707PD Orthotopic versus subcutaneous NET: tumor tissue characteristics result in different answers when ADC is used to validate early therapy response following Peptide Receptor Radionuclide Therapy (PRRT)

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Background: Preclinical studies in oncology are often performed in subcutaneous tumor models, where therapy success is validated by measuring changes in tumor size. We first characterized subcutaneous (sc) versus orthotopically grown neuroendocrine tumors of the pancreas (NET) with high versus low somatostatin receptor subtype 2 (SSTR2) by multimodal imaging and validated the apparent diffusion coefficient (ADC) as a potential biomarker for early therapy response following SSTR2-specific PRRT.

Methods: NET cells (native, SSTR2-transfected BON) were inoculated sc or orthotopically ($n = 20$) in SCID mice. Tumor characteristics were monitored using a small animal nanoScanPET/MRI: (T1/T2w anatomy, diffusion-weighted imaging, dynamic contrast-enhanced MRI, angiography; PET: Ga-68-DOTATOC, F-18-FDG. PRRT: ADC values and tumor growth were measured to monitor PRRT effects following Lu-177-DOTATOC injection.

Results: Native BON tumors showed different morphologic and metabolic patterns between sc and orthotopic tumors. Sc BON/SSTR2 tumors were similar to native sc BON tumors, while orthotopic BON/SSTR2 tumors were strongly growth delayed and developed necrosis at an early stage compared to native orthotopic BON tumors. Accept of the orthotopic BON/SSTR2 tumors, small tumors appeared solid with high FDG uptake. During tumor growth necrosis increased and FDG decreased. Perfusion was increased in orthotopic versus sc tumors (ktrans = 0,49 min^{-1} and 0,31 min^{-1}). Interestingly, Lu-177-DOTATOC uptake was ~4 times higher in sc than in orthotopic BON/SSTR2 tumors. While the ADC reflected the early effects of PRRT (first 9 days) precisely in orthotopic tumors, therapy response could not be validated by ADC in sc tumors due to initial high liquid content in the tissue.

Conclusions: Successful therapy validation presupposes precise knowledge about the used xenograft und the tumor morphology in order to allow correct interpretation of therapeutic effects. In particular, the orthotopic SSTR2- tumors do reflect the physiological situation better than sc tumors and allow to use the ADC as a potential biomarker for early validation of PRRT effects.

Legal entity responsible for the study: DKTK German Cancer Konsortium/DKFZ German Cancer Research Center

Funding: DKTK - German Cancer Konsortium, German Cancer Center (DKFZ)

Disclosure: All authors have declared no conflicts of interest.

1708P Anti-tumor activity of alectinib in the orthotopic in vivo imaging model with NCOA4-RET fusion positive tumor cells

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Background: The rearranged during transfection (RET) gene was discovered in 1985 as an oncogene produced by recombination during the transfection of NIH 3T3 cells with human lymphoma DNA. RET fusion genes were recently identified in a population of non-small cell lung cancers (NSCLCs). The most common (>80%) fusion partner for RET is KIF5B, followed by CCDC6, NCOA4, TRIM33, CLIP1, and ERC1. Recent clinical trials for RET fusion-positive NSCLC using vandetanib or cabozantinib demonstrated positive clinical response and considerable differential activities for RET inhibitors among fusion partners. Alectinib, an approved ALK inhibitor, is reported to inhibit KIF5B-RET and CCDC6-RET. However, the activity of alectinib with respect to RET with other fusion partners is unknown.

Methods: In the present study, we investigated the effects of alectinib on NCOA4-RET fusion-positive tumor cells (EHMES-10, a mesothelioma cell line) *in vitro* by MTT assay. We also examined the effect of alectinib utilizing orthotopic implantation model with EHMES-10 cells in the in vivo imaging model.

Results: Alectinib inhibited the viability of NCOA4-RET-positive EHMES-10 cells, as well as CCDC6-RET-positive LC-2/ad and TPC-1 cells. This was achieved via inhibition of the phosphorylation of RET and induction of apoptosis. Moreover, alectinib suppressed the production of thoracic tumors and pleural effusions in an orthotopic intrathoracic inoculation model of EHMES-10 cells. *In vivo* imaging of an orthotopically inoculated EHMES-10 cell model also revealed that alectinib could rescue pleural carcinomatosis.

Conclusions: These results suggest that alectinib may be a promising RET inhibitor against tumors positive for not only KIF5B-RET and CCDC6-RET, but also NCOA4-RET.

Legal entity responsible for the study: Kanazawa University

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1710P Cathepsin S regulates cell migration and invasion through mediating store-operated calcium entry and the focal adhesion proteins

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Background: Cathepsin S (CTSS), a lysosomal cysteine protease, plays an important role in inflammation, and it has been reported that it is also associated with angiogenesis and extracellular matrix (ECM) degradation promoting cell migration and invasion. Since CTSS is stably overexpressed in the different types of cancer cells, we explored a novel intracellular mechanism other than ECM degradation that regulates cell migration and metastasis.

Methods: Human oral cancer cells, OEC-M1, and breast cancer cells, MDA-MB-231, were used for this study. The expressions of CTSS were knockdown by siRNA transfection and the enzymatic activities were inhibited by highly-selective CTSS inhibitor, 58. The migratory and invasive abilities were determined by wound healing assay and transwell invasion assay, respectively. Microarray data and promoter prediction analysis were used to determine the intra-cellular targets of CTSS. Immunofluorescence assay was executed to evaluate STIM1 puncta formation and calcium influxes from store-operated calcium entry (SOCE) were measured by fura-2 calcium imaging. Western blot analysis was performed to detect the alteration of focal adhesion proteins.

Results: Our data showed that either CTSS knockdown with siRNA or activity inhibition could significantly decrease cell spreading area, and suppress cell migratory and invasive activities in both OEC-M1 and MDA-MB-231 cells. Moreover, inhibition of CTSS enzymatic activity resulted in the suppression of STIM1 aggregation and decreasing calcium influx from SOCE. Furthermore, downregulation of CTSS expression with siRNA could reduce the protein expression of three focal adhesion proteins, including CD29, CD104 and vinculin, which could be restored by CTSS transfection.

Conclusions: These results exhibit a novel intracellular molecular mechanism of CTSS mediating STIM1 aggregation and the calcium influx from SOCE to regulate the focal adhesion proteins, which are crucial for ECM interactions, cell migration and invasion.

Legal entity responsible for the study: Ministry of Science and Technology of Taiwan

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1711P Type VI collagen (COL6) as part of tumorgenesis: Focus on quantifying specific COL6 protein fragments in serum

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Background: Type VI collagen (COL6) is emerging as an important component of the tumor microenvironment. The rationale that COL6 derived protein fragments may possess pro-tumorigenic properties has ample precedent (e.g. endothrophin). Little is however known, regarding COL6 degradation fragments as biomarkers for cancer. Here we address the biomarker potential of three specific COL6 degradation fragments measured in serum: Pro-C6 (C-terminal of the α3 chain/endotrophin), C6Ma3 (MMP-generated neo-epitope on the α3 chain), C6M (MMP-generated neo-epitope on the α1 chain).

Methods: Pro-C6, C6Ma3 and C6M were measured by validated competitive ELISAs in serum from patients with various stage solid tumors prior to treatment and healthy controls (table).

Results: C6M and C6Ma3 were significantly elevated (Kruskal-Wallis test) in most cancer types compared to controls, whereas Pro-C6 was not (table). A trend ($p = 0.098$) toward higher Pro-C6 was seen in the late (3/4) vs early (1/2) stage (Mann-Whitney test), whereas no difference was seen with C6M ($p = 0.822$) and C6Ma3 ($p = 0.458$). AUROC was 0.89 ($p < 0.0001$) and 0.86 ($p < 0.0001$) and 0.59 ($p = 0.216$) for C6M, C6Ma3 and Pro-C6, respectively, when comparing all cancer types combined to healthy controls.

Conclusions: Specific type VI collagen fragments were increased in serum from cancer patients compared to healthy controls, and showed promising clinical accuracy. This clearly support COL-6 remodeling/degradation as an important component in understanding tumorgenesis. Future studies will determine biological and clinical applicability of quantifying various COL-6 fragments in serum in relation to cancer.

Legal entity responsible for the study: Nordic Bioscience

Funding: None

Table: 1711P

Cancer:	Breast	Colon	Gastric	Melanoma	NSCLC	Ovary	Pancreas	Prostate	SCLC	Healthy controls
n	8	6	7	7	10	8	4	10	7	21
stage	2-3	2-3	1-3	1-3	1-3	1-3	1-3	1-2	1-4	–
C6M[1] (p-value[2])	43.4 (**)	56.0 (**)	16.5 (ns)	31.2 (ns)	87.6 (****)	47.6 (**)	60.5 (*)	33.9 (ns)	49.5 (**)	12.0 -
C6Ma3[1] (p-value[2])	2.7 (**)	3.1 (**)	1.1 (ns)	2.3 (ns)	3.1 (****)	2.4 (ns)	2.9 (*)	2.3 (ns)	2.6 (*)	0.99 -
Pro-C6[1] (p-value[2])	7.2 (ns)	9.8 (ns)	7.4 (ns)	8.9 (ns)	8.4 (ns)	20.8 (ns)	10.6 (ns)	7.1 (ns)	9.2 (ns)	9.5 -

[1]mean, ng/ml;
[2]vs. healthy controls;
p-value *<0.005, **<0.01, ****<0.0001, ns: not significant

Disclosure: A. Wardak, N. Willumsen, D.J. Mogensen, S.H. Nielsen, C. Jensen, S. Kehlet, M.A. Karsdal: Employed by Nordic Bioscience involved in biomarker development

1712P The combination analysis of tumor infiltration lymphocyte with Neutrophil to lymphocyte ratio may predict prognosis of colorectal cancer in stage I-III

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Background: The tumor infiltration lymphocyte as local inflammation and neutrophil to lymphocyte ratio as systemic inflammation have been known as prognostic factors in colorectal cancer. But little is known about the correlation and impression of the local and systemic inflammation together on the prognosis of colorectal cancer. This study aimed to evaluate the effects of this combination on prognosis.

Methods: In a retrospective study, 206 patients from 2006-2015 with colorectal cancer after curative surgery have been investigated. the patients diagnosed with stage IV or simultaneously had secondary cancers were excluded. The pathological samples after surgery were studied for tumor infiltration lymphocytes (TIL) and other pathological features. Also neutrophil to lymphocyte ratio (NLR>2.38) was calculated from up to 3 days before surgery from peripheral blood. For analysis the combination of these markers, patients were divided to four groups for local inflammation or systemic inflammation predominantly (high TIL/High NLR, high TIL/Low NLR, Low TIL/High NLR and Low TIL/Low NLR) and then the overall survival (OS) and Disease free survival (DFS) for each group were calculated. Then compared with each other.

Results: For these identified patients the number of death events was 73and 133 were alive the median OS was 68 months(Range1 to 122) months .There was significant relationship between local and systemic inflammation (TIL and NLR) (p-value=0.0003), so that, when the local inflammation was predominantly and the systemic inflammation was dramatically low simultaneously, (high TIL/Low NLR) was associated with the best outcomes and improved the overall survival (mean OS = 72.56 month and HR:0.45) also low TIL was significant associated with poor prognosis on OS and DFS (p-value<o.ooo1) for both.

Conclusions: The analysis of combination of local and systemic inflammation may predict the prognosis of colorectal cancer in patients who underwent the curative surgery. So in future this unexpansive and available methods seem can be used for determining the prognosis for these patients and used as markers.

Legal entity responsible for the study: Seyyed Mohammad Reza Mortazavizadeh

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1713P Prognostic value of NK and T-lymphocyte markers in operable non-small cell lung cancer (NSCLC)

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Background: New therapies aimed at activation of T and NK cells expand NSCLC treatments options. It is conceivable that markers designating 'immune ignorant', 'immune excluding' or 'inflamed' tumor phenotypes may influence the effectiveness of specific immune therapies.

Methods: qRT-PCR was used to assess the levels of 48 mRNAs in frozen tumor tissue sections from 115 stage I-IIIA NSCLC patients (33% never-smokers, 75% lung adenocarcinoma) who underwent pulmonary resection, and in matched normal lung parenchyma. mRNA expression (normalized vs. 4 reference genes) was compared between groups that did (45%) and did not relapse.

Results: Low expression of *TIGIT* (p.adj=0.031) and *CTLA4* (p.adj=0.048) was correlated with shorter distant metastasis free survival after correction for multiple comparisons. In the subset of 75 lung adenocarcinoma cases, low expression of *TIGIT, NCR3, CXCR3, FASLG, CD96, CTLA4, PD1, FYB* and *FOXP3* was correlated with shorter distant metastasis free survival after correction for multiple comparisons (p.adj<0.042). Expression of *PD-1* (p = 0.016), *PDL-2* (p = 0.029) and *CTLA4* (p = 0.002) was significantly lower in relapsed vs. non-relapsed NSCLCs, whereas there was no difference for *PDL-1*. Expression of NK markers: *NCR3* (p = 0.006) and CD96 (p = 0.005), but not *NCR3-ligand 1* or *NKG2D, NKG2C* and *NKG2A* was significantly lower in relapsed vs. not relapsed NSCLCs. Expression of *CXCR3* and its ligands: *CXCL9* and *CXCL10* (chemoattractants for lymphocytes), but not *endothelin receptor type B*, was significantly lower in relapsed NSCLCs (p < 0.03), which could provide a plausible explanatory mechanism for lower expression of lymphocyte markers in tumours with propensity for metastases. *GITR, FOXP3 and CXCL9* expression was significantly higher in tumor samples vs. normal lung parenchyma (p.adj.<0.02). *NCR3, CXCR3 and FASLG* expression was significantly lower in tumor samples from smokers vs. never-smokers (p.adj<0.02). Samples of normal lung parenchyma from smokers were marked by higher expression of *PD-1* and *CD96* in reference to never-smokers (p.adj<0.04).

Conclusions: Non-inflamed NSCLC phenotype is associated with higher risk of distant metastases in early stage NSCLC. The non-inflamed phenotype is accompanied by lower expression of chemoattractants for lymphocytes. Expression of immune tolerance markers is increased in NSCLC compared to normal lung tissues.

Legal entity responsible for the study: Medical University of Gdansk

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Disclosure: All authors have declared no conflicts of interest.

1714P KRAS in non-small cell lung cancer

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Background: Disease heterogeneity with variable molecular mutations is one of the main contributory factors in non-small cell lung cancer (NSCLC). The goal of this study was to better understand the KRAS patients with co-occurring mutations.

Methods: We identified 60 patients with a diagnosis of NSCLC and a KRAS mutation in the COH Cancer Registry from 2009 to 2016. Next generation sequencing was performed.

Results: Of the 60 patients identified, 42 (70%) were Stage IV at diagnosis, 7 (12%) Stage I and 7 (12%) stage II and 4 (6%) Stage III. 47% (78) patients were smokers. Caucasian was the most common 44 (73%) racial group, followed by Asians 9 (15%), African-Americans 3 (5%), other 3(5%) and Pacific Islander 1 (1.7%). The average age at diagnosis was 67 (median 69.5) years; 30 patients (50%) were > 70 years, 23 (38%) patients were 51-69 years, and 7 (12%) 50 years or less. The most common histology was adenocarcinoma 52 (87%), then adenosquamous 3 (5%), large cell 2 (3%) and small cell, squamous cell and carcinosarcoma (1 each, less than 2% each). Majority had metastatic disease 52 (87%) with 20% (12) metastasis to brain, with average 1.6 metastatic sites. An average of 1.97 (range = 0-5) lines of therapy including chemotherapy, biologic agents or immunotherapy were received. 12 (20%) patients received immunotherapy, radiation in 28 (47%) and surgery in 22 (37%) with a median overall survival at 15 months. The most frequent molecular alteration was codon 12 mutation (47, 78%), followed by codon 13 (7, 12%) and codon 61 (6, 10%) mutations. The most

common co-occurring mutations in this cohort were TP53 (15, 25%), ATM (9, 15%), LRP1B (9, 15%), ARID1A (8, 13%), STK11 (8, 13%), ARID1B (7, 12%), TERT (7, 12%), EGFR (6, 10%), RBM10 (6, 10%), SPTA1 (6, 10%). We are currently evaluating the relevance of the Circos plot analysis for these mutations, clinical response to immunotherapy and potential biomarkers.

Conclusions: *KRAS* mutations are among the most common molecular alterations identified in NSCLC. The discovery of effective treatments targeting *KRAS* mutations has represented a challenge so far. Understanding the significance of co-mutations and their therapeutic implications, especially in response to immunotherapy agents represents an important step to develop better treatment options for *KRAS* mutated lung cancers.

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1715P PIK3CA mutation and PDL1 expression in lung squamous cell carcinoma surgically resected

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Background: Squamous-cell carcinoma (SCC) of the lung is the second most frequent histology in non-small cell lung cancer (NSCLC). Over the last decade new approaches targeting specific pathways in NSCLC have emerged but very few advances were made in its treatment. The PI3K-AKT-mTOR pathway is implicated in multiple cancer processes and *PIK3CA* mutations are being investigated in SCC as potential therapeutic target. The aim of the study was to evaluate the histological characteristics, mutations in *PIK3CA* and PD-L1 expression in these tumors.

Methods: Surgically resected lung SCC samples (FFPE) from 100 patients, stage I-III, were included in this study. Clinicopathologic characteristics included tumor size, TNM, smoking status, lymphovascular and pleural invasion, histopathological grade, stromal lymphoplasmacytic reaction and type of tumoral growing. DNA was isolated from 92 samples according to standard procedures and *PIK3CA* mutation analysis was done using Cobas 4800 platform. PD-L1 expression was analyzed in 74 cases by immunohistochemistry with PDL1 22C3 pharmDX assay. The PD-L1 expression was evaluated by tumor proportion scores (TPS) as IASLC guidelines.

Results: The mean age was 68 years (53-86), 14 females and 86 males. About staging: 53 patients had stage I, 27 stage II, and 19 stage III. 53% and 35% showed vascular and pleural invasion respectively. Low to moderate stromal lymphoplasmacytic reaction was found in 34% and severe in 11%. PI3KCA mutation was found in 9/92 (9,8%) patients: E545X (n = 2), E542K (n = 5), H1047X (n = 1), C420R (n = 1). PD-L1-expression was found in 31 out of 74 cases (42%): 14 cases with TPS between 1-49%; 17 cases with TPS >50%. 5/9 (55%) of PIK3CA mutated cases were PD-L1 positive (2 of them >50%). In PIK3CA non-mutated cases 26 out of 67 (39%) showed PD-L1 expression: 11 cases with TPS between 1-49%; 15 cases with TPS >50%.

Conclusions: *PIK3CA* mutation was found in 9,8% of SCC of the lung, most of them in exon 9. PD-L1 expression was found in 42% of the SCC in our series. 55% of *PIK3CA* mutated patients were positive for PD-L1 expression. No correlation has been found between PD-L1 expression and *PIK3CA* mutation in SCC. It is important to know more about the relation of these factors to select the patients for immunotherapy and new target agents.

Legal entity responsible for the study: IIS

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Disclosure: All authors have declared no conflicts of interest.

1716P TRKA expression and NTRK1 gene copy number across solid tumors

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Background: Neurotrophic Tropomyosin Kinase Receptor 1 (NTRK1) gene encodes for the protein Tropomyosin-related kinase A (TRKA). A deregulated activity of TRKA has been detected in cancer, leading to oncogenic activity. This can result from translocations, amplifications, deletions and point mutations involving the NTRK1 gene. The incidence of NTRK1 gene copy number gain (GCN) across solid tumors has not been investigated. We present here the results of an immunohistochemistry (IHC) screening for TRKA expression within the phase I ALKA-001 clinical trial. Clinical results of ALKA-001 clinical trial are not presented here.

Methods: Formalin-fixed paraffin-embedded (FFPE) consecutive samples of different solid tumors were tested for TRKA IHC staining. Samples showing TRKA IHC staining in at least 10% of cells were further studied by fluorescence in situ hybridization (FISH) to assess whether NTRK1 gene rearrangements were present and to assess GCN. All patients signed informed consent for molecular screening according to the phase I ALKA-001 clinical trial.

Results: 1043 samples were tested; annotation for histology was available in 1023. Most of the samples were colorectal adenocarcinoma (CRC) (n = 550, 53.8%) or lung adenocarcinoma (312, 30.5%). 24 samples (2.3%) were biliary tract carcinoma (BTC). Seventeen (1.6%) samples were characterized by TRKA IHC expression (4 weak, 8 moderate, 5 strong). By FISH, 1/17 (5.9%) displayed *NTRK1* gene rearrangement and 15 (88.2%) *NTRK1* GCN gain. Among samples harboring *NTRK1* GCN gain, 8 (53%) were lung adenocarcinoma, 3 (20.0%) BTC and 2 (13.3%) CRC. Five (33.3%) samples had concomitant ALK and ROS1 GCN gain. None of the lung adenocarcinoma (n = 8) had concomitant EGFR mutations. Both CRC samples (n = 2) harbored *KRAS* mutation. No correlation was found between grading of TRKA IHC staining and the number of *NTRK1* GCN.

Conclusions: NTRK1 GCN gain can be found in 1.6% of solid tumors. In particular, we found GCN gain in 2.6% of lung adenocarcinomas, without EGFR mutations, 0.4% of CRC and 17.6% of BTC even though a limited number of the latter histology was included in the analysis. The prognostic and translational therapeutic impact of this genetic alteration remains to be established.

Legal entity responsible for the study: Salvatore Siena

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1717P The correlation between MMR gene expression MSH2/MSH6 and VEGF A/VEGF B in gastro-esophageal cancer

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Background: VEGF proteins are key regulators of angiogenesis and targeting VEGF A led to inhibition of new blood vessels formation, with important therapeutic effects in various cancers. The roles of VEGF B are controversial; this peptide expression seems to inhibit apoptosis by suppressing many apoptotic/cell death-related genes and to facilitate metastasis by inducing vascular leakiness, leading to a high degree of tissue hypoxia that consequently activates DNA damage signalling pathways. MSH2/MSH6 is an important complex of proteins in DNA mismatch repair system and their altered expression could represent a response to the rapidly growing number of replication errors in a tissue with a high index of proliferation.

Considering that in certain conditions, DNA damage response products, such as H2AX, promote tumor growth and angiogenesis, in the present study we aimed to identify a common pattern of expression behavior between MMR genes MSH2/MSH6 and VEGF components (VEGF A and VEGF B), in order to use these genes as diagnostic markers in gastro-esophageal cancer.

Methods: mRNA levels of MSH2, MSH6, VEGF A, VEGF B were evaluated in tumoral and peritumoral tissues samples biopsied from 36 patients using qRT-PCR with specific TaqMan gene expression assays.

Results: VEGF A/VEGF B and MSH2/MSH6 mRNAs were expressed in both tumour and peritumour mucosa, with a tendency of tumoral up-regulation for VEGF A and MSH2/MSH6. When comparing the differences between tumoral/peritumoral expression level among the studied genes, we found that MMR and VEGF have a similar pattern of expression as follows: VEGF A gene expression correlates with MSH2 (rho Spearman = 0.4562; $p < 0.05$) and also, is similar to MSH6 (rho Spearman = 0.5082 $p < 0.05$); furthermore, VEGF B gene expression is correlated with MSH2 expression (rho Spearman = 0.5350 $p < 0.05$), with a very strong correlation between MSH6/VEGF B expression (rho Spearman = 0.6730 $p < 0.0001$).

Conclusions: Our results indicate a possible crosstalk between DNA mismatch repair and VEGF signaling pathways, providing new insight into understanding the potential connection of VEGF B and MSH6 in carcinogenesis.

Legal entity responsible for the study: University of Medicine and Pharmacy of Craiova, Romania

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Disclosure: All authors have declared no conflicts of interest.

1718P Liver-type glutaminase (GAB) suppresses malignant phenotype of glioblastoma cells

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Background: Glutamine (Gln) plays a pivotal role in the metabolism of tumors of different including glioblastoma (GBM), the most aggressive brain tumor. Glutaminase (GA, EC 3.5.1.2) converts Gln to glutamate (Glu) and ammonia. GA is encoded by two genes: *GLS* and *GLS2*, encoding kidney-type isoforms (KGA and GAC) and liver-type isoforms (GAB and LGA), respectively. Kidney-type isoforms promote cell proliferation, while the liver-type isoforms relate to quiescent state of cells. In GBM *GLS* is highly expressed, while *GLS2* is hardly detectable. Transfection of human GBM T98G cell line with a sequence encoding GAB is known to decrease their survival, proliferation index and migration and sensitizes them to damage by hydrogen peroxide. To examine whether the mode of action of GAB extends to other GBM cell lines, the effect of GAB transfection of U87MG, U251MG and LN229 cells with GAB was assessed.

Methods: Mitochondrial activity was determined by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) conversion (details in M. Szeliga et al., Glia, 2009). Cell proliferation was measured by a commercially available ELISA kit based on the detection of BrdU (5-bromo-2'-deoxyuridine) incorporated into the genomic DNA. Migration was analyzed using the scratch assay. The tip scratch of cell monolayer was photographed under Juli Smart cell analyzer and measured after 0 and 24 h. Ability to form colonies was assessed after 14 days of culture following Giemsa staining of fixed cells.

Results: Transfection with GAB: i) decreased mitochondrial activity, proliferation and colony formation ability of U87MG cells ii) inhibited ability of U251MG cells to form colonies iii) decreased mitochondrial activity, proliferation, migration and colony formation ability of LN229 cells. All transfected cells were more sensitive to hydrogen peroxide as compared to the controls.

Conclusions: Suppression of malignant phenotype and their sensitization to hydrogen peroxide damage by GAB transfection appears to be a feature common to all the glioblastoma cell lines so far studied.

Legal entity responsible for the study: Jan Albrecht, PhD

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Disclosure: All authors have declared no conflicts of interest.

1719P Alteration of p53 mRNA expression in neuroblastoma and its impact in disease outcome

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Background: Neuroblastoma is frequent childhood malignant tumor with high clinical heterogeneity. Despite the rare mutations of *TP53* gene, p53-mediated pathway is often inactivated in neuroblastoma. The significance of MDM2, p53 direct antagonist, overexpression in neuroblastoma clinical course and outcome has been already established. But still remain patients with favorable clinical features and poor disease outcome.

Methods: The case group comprised 68 children with neuroblastoma (mean age: 36.7±4.7 months; primary tumors: 88%; MYCN+: 39%; MDM2 overexpressed: 70%). p53 mRNA expression level (EL) was analyzed in tumor samples with qRT-PCR and evaluated by the ΔΔCt method according to control *GAPDH* mRNA EL.

Results: We established that the value of p53 EL in neuroblastoma cells varied in wide limits. Significantly lower p53 EL was detected in recurrent and metastatic tumor samples comparing to primary tumors ($P = 0.001$). Insignificant increase of p53 EL in patients with unfavorable clinical and biological features (late occurrence age, IV stage, MYCN amplification) was observed. However, we revealed significant increase of p53 EL in MDM2 overexpressed tumors ($P = 0.007$). With ROC-analysis we assessed the optimal criterions for distribution of patients according to p53 expression (OC:>1.18 a.u., $P = 0.04$, AUC:0.69 for high and OC:<0.09 a.u., $P = 0.006$, AUC:0.84 for low MDM2 expression). We have analyzed 3-year event-free survival (EFS) of patients with neuroblastoma and established 100% EFS survival for patients with low MDM2 and high p53 expressions, while in other groups significant decrease in survival was observed ($P < 0.05$). EFS rates of patients with low p53/high MDM2 and high p53/low MDM2 expressions were similar (27.7% and 33.3%) and for p53/MDM2 overexpressed tumors it was only 18.2% ($P < 0.05$).

Conclusions: Regulation of p53-mediated pathway is complex and multicomponent system. Alteration of p53 EL is independent from clinical features marker of neuroblastoma. Analysis of p53/MDM2 co-expression provides the possibility for better neuroblastoma outcome prediction.

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1720P Downregulation of BRCA1 protein in clear cell renal cellular carcinoma

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Background: Around 75% of renal cancer in adult kidney is clear cell renal cellular carcinoma (ccRCC). This type of cancer is characterized by lipids overacumulation and mutations in VHL (around 90% cases), BAP1 and PBRM1 genes as well as stabilization of HIF1α transcription factor. Additionally, metabolic switch to aerobic glycolysis and aberration in TCA cycle was observed in ccRCC independently on the stage of the disease. Moreover, the mTOR pathway hyperactivation and downregulation of AMPK pathway featured the ccRCC. This type of cancer is highly resistant to classical chemotherapy. BRCA1 is tumor suppressor gene, mutation in this gene is associated with breast and ovarian cancer. BRCA1 is a protein involved in DNA repair and apoptosis also interacts with BRG1 – core subunit of SWI/SNF chromatin remodeling complex. BRCA1 is transcribed from bidirectional promoter together with NBR2 – lncRNA. Interestingly, NBR2 interacts with AMPK and is downregulated in ccRCC. CTCF is a protein which binds Topologicaly Associated Domains, and CTCF binding site was found in BRCA1/NBR2 promoter region.

Methods: Immunohistochemistry (IHC) on paraffin embedded clinical samples for BRCA1 and BRG1 core subunit of SWI/SNF complex, comparative transcriptomic study, co-immunoprecipitation (Co-IP) and chromatin immunoprecipitation (ChIP) method were used in this work.

Results: In this study we found downregulation of BRCA1 and BRG1 proteins in ccRCC patient samples independently on stage of the disease. Interestingly, downregulation of BRG1 was more severe in samples with strong lymphocyte infiltration. By contrast, downregulation at the transcript level was observed for BRG1 encoding gene but not for BRCA1. BRG1 and CTCF co-precipitated from cancer cells, indicating the existence of co-interaction between CTCF, BRG1 and BRCA1 proteins. Additionally, overexpression of BRG1 caused increased expression of CTCF in human cells. We also found that BRG1 targets both CTCF and BRCA1 genes.

Conclusions: BRCA1, BRG1 and CTCF module is dysregulated in ccRCC cells independently on Fuhrman grade and stage of the disease. This missregulation can have a brought spectrum of changes including 3D chromatin structure, transcription, epigenetic and others.

Legal entity responsible for the study: Elzbieta Sarnowska

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Disclosure: All authors have declared no conflicts of interest.

1721P The role of PD-L1 in a high-grade invasive human oral squamous cell carcinoma microenvironment

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Background: Blockade of the programmed-death 1 receptor (PD-1)/programmed-death ligand (PD-L1) pathway efficiently reduces tumour growth and improves survival. Durable tumour regression with blockade of the PD-1/PD-L1 checkpoint has been demonstrated in recent clinical studies. Oral squamous cell carcinoma (OSCC) is highly immunosuppressive, and PD-L1 expression has been proposed as a potential mechanism responsible for this phenotype. Despite the fact that anti-PD-1 treatment can produce durable responses, such therapy appears to benefit only a subset of patients. Thus, it is important to understand the mechanisms underlying the regulation of PD-L1 expression in the OSCC microenvironment.

Methods: The subjects were patients with primary OSCC who underwent surgical resection at the Kanazawa University Hospital between 1998 and 2008. And, three human oral squamous cell carcinoma cell lines established from tumor biopsies with different grade of invasive abilities were used: OSC-20, OSC-19 and TSU.

Results: We showed that PD-L1 expression in high-grade invasive OSCC cell lines was lower than that in a low-grade invasive OSCC line and found a close correlation between PD-L1 expression and the epithelial-mesenchymal transition (EMT). PD-L1 expression was upregulated in macrophages and dendritic cells (DCs) in high-grade invasive human OSCC tissues or co-cultured with mesenchymal-phenotype OSCC cells in vitro. TLR4-inhibitory peptide successfully suppressed PD-L1 upregulation on macrophages and DCs co-cultured with mesenchymal-phenotype OSCC cells, suggesting that some EMT-induced tumour antigen is critical for PD-L1 induction on tumour-associated macrophages and DCs.

Conclusions: Further studies are necessary to explore the impact of EMT on the tumour immune microenvironment and to identify potential biomarkers for selecting

patients who might preferentially benefit from PD-1/PD-L1 blockade or immunotherapies more broadly.

Legal entity responsible for the study: Kanazawa University

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1722P Loss of SWI/SNF chromatin remodelling complex is linked to advanced urinary bladder cancer

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Background: Bladder cancer originated from urothelium belongs to the top ten among all tumors. Various factors like genetic and molecular defects, appearance of different tumors in the family, previous genitourinary disorders and exposure to chemical compounds are reported as potential causes of this type of cancer. It has been reported that TP53, p21 or Ras mutations and epigenetic alterations of genes coding for these oncogenes are involved in the aetiology of urothelium originating bladder cancer. Additionally, the TCGA study indicated that such important regulatory pathways/machineries like these controlling cell cycle; (PI(3)K)/AKT/mTOR signaling involved in the metabolism control; and chromatin modificators including SWI/SNF chromatin remodeling complex (CRC) are affected in this disease.

Methods: Immunohistochemistry (IHC) on paraffin embedded clinical samples for SWI/SNF core subunits and key enzymes involved in metabolism control, comparative transcriptomic study and confirmatory quantitative real-time PCR (qRT-PCR) were used in this work.

Results: In this study we found a substantial decrease of protein levels of SWI/SNF core subunits in bladder cancer clinical samples. Subsequently, we performed reanalysis of transcriptomic data for clinical samples obtained from GEO database and confirmatory assessment of the transcript level in clinical samples. This analysis showed that the reduced protein level of SWI/SNF core subunits observed in advanced bladder cancer is likely caused by the decreased abundance of corresponding transcripts. We also found that the SWI/SNF complex interacts in human cells with key proteins involved in the control of energy status and glucose metabolism. The IHC analysis indicated altered abundance of these enzymes in cancer cells when compared to normal urothelium consistently to strong metabolic alterations characteristic for this type of cancer.

Conclusions: The down-regulation of SWI/SNF complex on both transcript and protein level, and decreased activity of its partner proteins link the molecular features with metabolic alterations observed in this type of cancer.

Legal entity responsible for the study: Michal Szymanski

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Disclosure: All authors have declared no conflicts of interest.

1723P The role of hepatocyte nuclear factor 1 homeobox B (HNF1B) loss in chromophobe RCC (ChRCC) development

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Background: ChRCC is characterized by dramatic chromosomal copy number (CN) changes. Currently, no model is available to precisely elucidate the molecular drivers of this rare tumor. HNF1B is a master regulator of gene expression, and both mutated *HNF1B* and downregulated HNF1B protein levels have previously been described in ChRCC.

Methods: We queried The Cancer Genome Atlas ChRCC database and analyzed tissue microarray data to determine the relative levels of HNF1B in ChRCC versus other RCC subtypes, and assessed the prognostic impact of dual *HNF1B* and *TP53* loss. We knocked out *Hnf1b* in proliferating murine embryo fibroblasts (MEFs) and human ACHN cells and measured the effect on gene and protein expression of checkpoint regulatory proteins, spindle integrity, and aneuploidy. We then performed dual knockdown of *HNF1B* and *TP53* and assessed cellular behavior.

Results: We found that *HNF1B* transcript and HNF1B protein were downregulated in the majority of ChRCC in TCGA, and the magnitude of *HNF1B* loss is unique to ChRCC. Additionally, we observed a strong correlation between reduction of *HNF1B* expression and aneuploidy in ChRCC patients. In MEF cells deficient in *Hnf1b*, we observed the development of aneuploidy. *Hnf1b* deficiency also reduced spindle checkpoint protein (MAD2L1, BUB1B) and cell cycle checkpoint protein (RB1 and p27) expression, and altered chromatin access of *Mad2l1*, *Bub1b* and *Rb1* genes. Coordinate loss of *Bub1b* and *Rb1* recapitulated the polynuclearity and larger cell size seen with *Hnf1b* depletion. TCGA data also showed that *TP53* is mutated in 33% of ChRCC whose *HNF1B* expression was repressed, and the combination of *HNF1B* loss with *TP53* mutation was associated with poor prognosis. The combination of *HNF1B* loss with *TP53* inactivation led to increased cell proliferation and increased aneuploidy, providing evidence that coordinate loss of *HNF1B* and *TP53* may enhance cellular survival and engender an aggressive ChRCC tumor phenotype.

Conclusions: *HNF1B* deficiency is a major driver of chromosomal instability in ChRCC and lethality is associated with subsequent *TP53* loss. Further development of model systems with combined *HNF1B/TP53* loss will accelerate the development of treatments specific for ChRCC.

Legal entity responsible for the study: UT MD Anderson Cancer Center

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Disclosure: All authors have declared no conflicts of interest.

1724P Some mechanisms of increasing malignancy of B16/F10 melanoma in female mice with chronic pain

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Background: The impact of chronic pain (CP) on the growth and development of tumors is poorly studied. However, one of the main goals of cancer therapy is the relief of chronic pain, a complex symptom based on combined pathophysiological mechanisms. Our aim was to study the influence of CP on melanoma growth in female mice and to determine levels of the VEGF family members in the tumor (T), its perifocal zone (PZ) and in the skin.

Methods: The study included 64 female C57BL/6 mice; B16/F10 melanoma was transplanted under the skin on the back of animals in the main group 2 weeks after sciatic nerve ligation. Mice with melanoma without CP were used as the controls. Levels of VEGFs: A, C, R1 and R3 were determined by ELISA (BenderMedSystem, Austria).

Results: The life span of mice with melanoma and CP was 1.5 times shorter than the control group. Melanoma in mice with CP was more aggressive, and metastases occurred after 1 week vs. 4 weeks in the controls. The rate of metastasis was higher (100% vs. 60% in the controls); melanoma with CP spread to multiple organs and caused unusual metastases to the heart and uterus. The rapid and specific development of B16/F10 melanoma in mice with CP was accompanied by increased levels of VEGF-A, -C and -R1 in T, PZ and the skin, with their maximal accumulation in T in week 1. The VEGF-A level continued to increase in T and PZ (PZ<T) in week 2; VEGF-C and VEGF-R1 levels increased in PZ only and decreased in T and skin (T<PZ). The VEGF-A levels were equally highest in both T and PZ, while VEGF-C and VEGF-R1 content in T was higher than in the skin and higher in PZ than in T. The VEGF-R3 level increased in T of mice without CP and was higher in T than in PZ, while in mice with CP its content in T was lower than in PZ. Levels of VEGF-R1 (in all tissues) and VEGF-R3 (in the skin and PZ) decreased in mice with CP in week 3.

Conclusions: CP shortened the life span of female mice with melanoma and enhanced the aggressiveness of B16/F10 melanoma metastases. The activation of angiogenesis in T and PZ can be considered as one of the mechanisms of the neoplastic progression.

Legal entity responsible for the study: Rostov Research Institute of Oncology

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1725P Impact of global epigenetics machinery on clinical outcome of colorectal cancer patients treated with fluoropyrimidine-based therapy

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Background: The pathogenesis of colorectal cancer (CRC) is complex and influenced by many factors related to genetic, epigenetics and chronic inflammatory processes.

Methods: This is a prospective study, conducted on 102 Egyptian patients, diagnosed with CRC. Blood samples were collected at baseline and after 3 & 6 months of receiving fluoropyrimidine (FP) based therapy. DNA methylation was measured by LC/MS/MS

spectroscopy, acetylated histones (H3) and (H4) were measured by ELISA and RNA expression of FP metabolizing enzymes (TS, TP and DPD), DNA methyl transferases (DNMT3A and B) in addition to inflammatory markers (COX2, IL6, and IL1B) by qRT-PCR.

Results: The median age of the studied patients was 46 years, 47% of them were ≤ 45 years. Forty patients (38.8%) had rectal cancer, they exhibited significant H3 hyperacetylation and upregulation of COX2 and IL1B along with significantly lower median overall survival compared to colonic patients *(14.6 versus 23 months respectively)*. FP therapy produced significant decrease in global methylation, acetylated H3 & H4 levels, downregulation in TP and DNMT3B but significant upregulation in TS and DPD over treatment time. Significant positive correlations were found between global methylation and IL1B (r^2= *0.25, P= 0.01)*, acetylated H3 with DPD and COX2 (r^2= *0.28, P= 0.02 and* r^2= *0.27, P= 0.03 respectively*) and 5 methylated cytosine content (5MC) with DNMT3A and IL6 (r^2= *0.25, P= 0.04 and* r^2= *0.34, P= 0.004 respectively)*. Overexpression of COX2 > 17 had a significant poor prognostic effect on overall and event free survivals (HR = 0.58, *P= 0.003* and HR = 0.72, *P= 0.008* respectively). Also patients who had global methylation> 30 showed significant reduced event free survival by 39% (*P= 0.04*).

Conclusions: Global methylation and H3 acetylation regulated COX2, IL6 and IL1B which were not affected by the therapy, however H3 upregulated TS and DPD. Rectal cancer patients showed significant H3 hyperacetylation, upregulation of COX2 and IL1B along with significant lower overall survival.

Legal entity responsible for the study: National Cancer Institute, Cairo University

Funding: National Cancer Institute, Cairo University

Disclosure: All authors have declared no conflicts of interest.

1726P Comparison of breast cancer subtypes between young and elderly women

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Background: Breast cancer(BC) are increasingly recognized as heterogeneous disease based on expression of receptors for estrogen (ER), progesterone (PR), and human epidermal growth factor receptor 2 (HER2). There are four main subtypes of BC with differing tumor characteristics and different risk factors, treatment options and prognoses. Few data exist on the frequency of molecular subtypes in young and older women. The purpose of this study is to compare the distribution of the BC subtypes in young and elderly patients.

Methods: BC during the period 2013 to 2015 including ER/PR and HER2 status, was obtained from the Georgian main histopathology laboratories all over the country. We analyzed 1003 women with BC included 85 women aged 20 to 39 years (YA's), 118 women aged 40 to 45 years (older premenopausal),665 women aged 46-70 (postmenopausal) and 135women older than 70 years (elderly group) at diagnosis. Incidence rates were calculated by subtype (triple-negative; HR +/HER2 -; HR +/HER2 +; HR -/HER2 +), and differences in subtype characteristics by age groups were evaluated.

Results: The incidence of BC in YA's was 8,5%. The most common BC subtype was HR +/HER2- among all age groups, and HR -/HER2 + was the least; however, the relative contribution of each subtype varied within age categories. In YA's HR +/HER2 - was the most commonly diagnosed subtype (62%), followed by HR +/HER2 + (15%), triple-negative (12%) and HR -/HER2 + (11%). Statistically no significant difference of BC subtypes was observed in age groups. HR +/HER2 - subtype was lesser in YA's than in elder population (62% vs 73%), but statistically non-significant (p = 0.19) and there was not significant difference in prognostically "unfavorable" subtypes (HR-/HER2+ and triple-negative) (23% vs 17%) (p = 0.134; (CI) 95%: 0.09 to 1.71). Surprisingly no difference of Triple-negative BC was observed in YA and elderly groups (12% vs 13%).

Conclusions: The distribution of breast cancer subtypes among young adults didn't vary from that observed in older women. Our study results seem to be in contradiction with other studies previously reported in literature. Future studies should consider whether distribution of breast cancer subtypes influences long-term survival in young compared with older women.

Clinical trial identification: GYO 02/17

Legal entity responsible for the study: Georgian Group of Young Oncologists

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1727P Distribution of the PAM50 breast cancer subtypes within each pathology-based group: a combined analysis of 15,339 patients across 29 studies

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Background: Current classification of breast cancer in the clinical setting is based on pathology-based biomarkers such as hormone receptors (HR) and HER2. More recently, identification of the intrinsic molecular subtypes (IS) within each pathology-based group (i.e. HR+/HER2-, HR+/HER2+, HR-/HER2+ and triple-negative [TN]) is revealing clinical value. The objective of this study is to assess the distribution of the IS within each pathology-based group in a large series of breast cancer.

Methods: Twenty-nine studies were identified from the literature (2009–2017) in which IS and pathology-based data were reported. HR was evaluated by immunohistochemistry (IHC) and HER2 by IHC and/or FISH according to standard criteria. Pathology-based groups were divided into 4 groups: HR+/HER2-, HR+/HER2+, HR-/HER2+ and TN. IS (Luminal A [LumA], Luminal B [LumB], HER2-enriched [HER2-E], Basal-like [BL] and Normal-like) were identified using the research-based, or the standardized, PAM50 gene expression-based assay.

Results: PAM50 and pathology data was available in 15,339 patients. The distribution of the PAM50 IS within each IHC-based group is shown in Table 1. Within HR+/HER2- group (n = 9,768), non-luminal subtypes (HER2-E and BL) represented 5.6% and 2.2%, respectively. Within HR+/HER2+ group (n = 1,727), HER2-E and BL represented 29.2% and 2.1%, respectively. Within HR-/HER2+ group (n = 1,332), non-HER2-E subtypes (Luminal A/B and BL) represented 9.3% and 13.8%, respectively. Finally, within TN (n = 2,512), non-BL subtypes (Luminal A/B and HER2-E) represented 5.9% and 11.1%, respectively.

Conclusions: Our results confirm previous observations that all IS are represented within each pathology-based group. Based on our observations, future clinical trials in unselected breast cancer patient populations should be sufficiently powered to address the prognostic and predictive ability of the IS.

Legal entity responsible for the study: Hospital Clinic Barcelona. August Pi I Sunyer Biomedical Research Institute (IDIBAPS)

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1728P Genetic association of matrix metalloproteinase MMP- 1, MMP-3 and MMP-9 Genes with HCV-related hepatocellular carcinoma in Egyptian patients

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Background: Hepatocellular Carcinoma (HCC) is one of the most frequent cancers in Egypt where there is high prevalence of infection with the Hepatitis C virus (HCV). Matrix metalloproteinases (MMPs) are multifunctional proteins that play an important role in cell development, differentiation, inflammation and angiogenesis. Polymorphisms in MMPs genes might be involved in development of HCV related HCC. The aim of this study was to explore the relationship of gene polymorphisms in MMP-1,3 & 9 with liver cirrhosis and HCC patients.

Methods: The study included 128 subjects enrolled from Menoufia University Hospital inpatients and outpatients clinics from the Department of Clinical Oncology & Nuclear Medicine and Department of Tropical Medicine in the period between October 2015

Table: 1727P

IHC-Based		PAM50 intrinsic subtype distribution (%)				
n = 15,339	%	LumA	LumB	HER2-E	BL	Normal
HR+/HER2-	63.68	54.47	34.41	5.64	2.24	3.24
HR+/HER2+	11.26	34.45	30.57	29.18	2.08	3.71
HR-/HER2+	8.68	6.91	2.40	69.74	13.81	7.13
HR-/HER2-	16.38	3.53	2.39	11.15	78.23	4.70

and August 2016. Patients were classified into three groups. Group I: 48 patients with HCC in addition to liver cirrhosis, including 26 males and 22 females with a mean age of 58.60±5.29; Group II: 50 patients with liver cirrhosis, including 26 males and 24 females with a mean age of 56.74±5.21; Group III: 30 healthy subjects as controls, including 15 males and 15 females with a mean age of 56.30 ±7.30. Diagnosis of HCC was performed using two imaging methods (abdominal US & triphasic CT). All subjects except controls were positive for serum HCV RNA. Liver function tests, AFP & CHILD score were assessed. Gene polymorphisms were analysed using PCR-RFLP.

Results: HCC patients had higher mutant G2G2 (35.4%) and G2 allele (62.5%) of the MMP-1 gene than patients in both cirrhotic ($P < 0.05$) and control groups ($P < 0.001$). In addition, for the MMP-3 gene, HCC patients had the most noteworthy predominance of mutant 5A/5A (22.9%) and 5A allele (52.1%) compared to the cirrhotic ($P < 0.05$) and control groups ($P < 0.001$). The results of MMP-9 gene analysis uncovered a higher frequency of the mutant TT genotype and T allele in both HCC (56.3% and 74% respectively) and cirrhotic groups (10% and 35% respectively) compared to the control group. In HCC patients, we detected a significant correlation between heterozygote G1/G2 and G2/G2 of the MMP-1 gene and homozygote TT of MMP-9 with a higher CHILD score, tumor size and stage ($P < 0.05$). Moreover, MMP-3 5A/6A was associated with a higher CHILD score, portal vein thrombosis and stage ($P < 0.05$) compared to other genotypes.

Conclusions: Gene mutations in MMP-1,3, 9 may be involved in progression of liver cirrhosis and risk relationship for HCC development.

Legal entity responsible for the study: Menoufia University

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1729P Heterogenity of epigenetic and EMT marks observed in hepatocellular carcinoma with keratin 19 proficiency

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Background: The expression of keratin 19 (K19) has been proposed as a novel predictor for poor prognosis in patients with hepatocellular carcinoma (HCC). However, the cell origin of K19-proficient HCC remains unclear. Herein we tried to reveal the cell origin of K19-proficient HCC by tracing epigenetic footprints in cultured cells and clinical materials.

Methods: The KRT19 gene, which encodes K19, has a CpG island in promoter region and therefore implicates DNA methylation as a potential epigenetic process for K19 expression. Firstly, we examined epigenetic alterations in K19-positive HCC cell lines. Next, from a panel of 564 surgically resected HCCs, we clarify the clinicopathological relevance of K19-preficent HCCs by analyzing robust methylation analyses in KRT19 promoter region and LINE-1 in comparison with other cholangiocytic (K7), hepatocytic markers (HepPar-1 and Arginase-1), EMT markers (E-cadherin and vimentin), and a signal pathway associate with biliary differentiation (NOTCH-1).

Results: In vitro, although methylation in KRT19 promoter was associated with K19 deficiency, 5-aza-dC treatment failed to re-expression of K19. From 564 surgically resected HCCs, a cohort of 125 HCC patients was selected and analyzed after exclusion of HCC with recurrence, TNM stage as IIIB or more, preoperative therapy, transplantation, and combined hepatocellular-cholangiocarcinoma. In this cohort, K19 expression was found in 29 HCCs (23.2%), and corresponded with poor survival following surgery ($P = 0.025$) and extrahepatic recurrence free survival ($P = 0.017$). Compared with K19-deficient HCCs, the lower methylation level in KRT19 promoter was observed in K19-proficient HCCs ($P<.0001$). Instead, HCC with genome-wide hypermethylation in LINE-1 was frequently observed in K19-proficient HCCs ($P = 0.0079$). Additionally, K19 proficiency was associated with K7 proficiency ($P = 0.043$), and reduced both E-cadherin and HepPar-1 expression ($P = 0.043$ and$<.0001$, respectively).

Conclusions: K19-proficient HCC showed the poor prognosis owing to extrahepatic recurrence and the molecular signatures were different from K19-deficeint HCC, providing novel insights of heterogeneity underlying development of HCC with extrahepatic metastasis.

Legal entity responsible for the study: Takeshi Nagasaka

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1731P Rare malignancy rare site: Extranodal lymphomas

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Background: Extranodal Non Hodgkins Lymphoma (NHL) constitutes one quarter of all NHL cases. Oral cavity and breast represent 2 such uncommon sites.

Methods: Clinical and treatment details of patients with extranodal lymphomas who underwent treatment at our center were collected. Diagnosis was established by excision biopsy or by punch biopsy from the lesion. Histopathological examination (HPE) and immunohistochemistry (IHC) were performed. For staging, patients underwent positron emission tomography (PET) with computed tomography (CT) scan of the whole body.

Results: Case 1: A 32-year old male presented with complaints on the right-side base of tongue and difficulty in swallowing since 20 days. On examination, a nodular swelling was seen over the right side posterior one third of tongue going up to base of tongue. Punch biopsy from the tongue lesion was suggestive of NH. IHC showed CD 3 - positive, CD 30 - positive, ALK 1 - positive and CD 20 - positive with a final report of anaplastic lymphoma kinase (ALK) positive ALCL. Whole body PET-CT showed localized metabolic uptake in the tongue and in the right cervical lymph node - level II. A final diagnosis of ALK positive ALCL - stage IE was made. Case 2: A 22-year old female presented with complaints of lump in the right breast since 10 weeks. On examination there was a lump in the right breast measuring 3 x 2 cm in the lower outer quadrant and no other palpable lymphadenopathy. On evaluation, wide local excision of the lump was suggestive of a round cell tumor. IHC done showed the neoplastic round cells to be positive for CD 20, PAX5, CD 10 with a Ki 67 of 80% and BCL 2, MUM 1 - negative. Bone marrow examination was positive for lymphomatous deposits. Whole body PET-CT showed metabolically active sub-centimetric right axillary lymph node enlargement with diffuse hypermetabolism along axial bone marrow.

Conclusions: Only 11 previous cases of oral ALCL have been reported. Primary breast lymphoma is a rare disease, accounting for only 0.4-0.5% of all breast malignancies, 0.38-0.7% of all NHL. Extranodal NHL can occur at any site and keeping an open mind is the most important pre-requisite for making a diagnosis. Modern diagnostic tools such as IHC is mandatory for diagnosis and management of extranodal NHL.

Legal entity responsible for the study: Haryana Medical Council

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1732P Descriptive analysis of families with TP53 mutations: Is there a genotype/phenotype correlation?

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Background: Li-Fraumeni syndrome (LFS) is a rare and serious hereditary cancer syndrome caused by germline mutations in the TP53 gene. Our objective is to review the molecular and clinical characteristics of our LFS families.

Methods: Retrospective descriptive analysis. Molecular germinal diagnosis was done either by Sanger or NG Sequencing (Trusight Cancer, Illumina); Large Genomic rearrangements were tested by MLPA (MRC Holland).

Results: Among 4952 non-related families registered in our multidisciplinary program, 395 are *BRCA1/2* families and 36 haver other molecular diagnoses with 7/36 confirmed *TP53* families. Twenty-nine pts were reviewed, including 2 male carriers, (36, 40 years) that haven't developed cancers yet. Forty-one tumours were registered (median of 1,41 tumours/carrier, 0–4). Female/male was 2:1. Median age for the first tumour was 24 years (1-45) in the index cases and 35 (1,5-61) in relatives ($p > 0,05$). Breast cancer (BC) (34% of cancers/48% pts) and sarcomas (31% of cancers/44% pts) were the most common malignancies. For BC cases hormone receptor status was confirmed in 8/14 (positive in 6/8, simultaneous HER2 positivity in 2 cases). Median age of death was 40 (34-58). Most mutations were missense (5 - 2 dominant-negative affecting the DNA binding domain: c.743G>A, p.R248Q and c.725G>A, p.C242Y), none was recurrent and the only frequent mutation observed was c.743G>A, p.R248Q. One of the missense and the 2 frameshift mutations have never been described as germinal: c.481G>A, p.A161T; c.86del, p.N29Tfs*15 and c.990del, p.Q331Rfs*14 Chompret criteria were met in 6/7 (85%) of cases and didn't identitfy a breast cancer only family, with 3 consecutive generations affected.

Conclusions: Our data confirms the heterogeneity and complexity of malignancies and mutations in LSF. Breast cancer and sarcomas were the most frequent cancers and missense, non-recurrent mutations were mostly observed. In this study c.481G>A, p.A161T; c.86del, p.N29Tfs*15 and c.990del, p.Q331Rfs*14 are, for the first time, identified as germinal mutations. At this time no genotype-to-phenotype correlation could be confirmed. Chompret's criteria had only 85% sensitivity for the identification of TP53 families.

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